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VECTORCARDIOGRAMS OF NORMAL AND PREMATURE BEATS IN DIFFERENT LEAD SYSTEMS

BY

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Received April 5, 1954

From previous experiments (Burger, van Milaan, and Den Boer, 1952) it has appeared that the correspondence of vectorcardiograms registered with different lead systems is not always satisfactory. The question may be raised as to the cause of this. A bad correspondence may be ascribed to: (A) an abnormal shape or electrical conduction of the thorax; (B) a very large heart; or (C) other causes.

In some cases, in which the correspondence was conspicuously bad, fluoroscopy excluded an abnormal position or size of the heart as the cause. In deciding between these three possibilities the comparison of normal beats and ventricular premature beats can give us some further information. By means of premature beats, nature enables us to make observations in cases in which the excitation proceeds through the heart in quite different ways, while the surroundings of the heart remain entirely unaffected.

Method. Vectorcardiograms were registered in 16 subjects among whom there were some with a pathological vectorcardiogram. In most of them only one type of ventricular extrasystole was observed. When more than one type was present, only the frequently occurring type was used. In each subject vectorcardiograms were registered with the lead systems B_1, R_2, and W_4 (Burger, van Milaan, and den Boer, 1952).

In system B_1 the electrodes are connected to the left arm, right arm, and left leg, while a fourth electrode is placed on the sternum at the level of the axilla. In R_2 one electrode is connected to the left leg and the other three are at the level of the axilla; one of them is placed centrally on the vertebral column, and the others symmetrically on the thorax at a distance of 50 per cent of the thorax breadth. In both systems the components of the heart vector are linear combinations of the leads with coefficients that have been determined with the aid of a phantom. In system W_4, proposed by Wilson *et al.* (1947), three electrodes are connected to the arms and the left leg, while the fourth is placed on the back at the level of the seventh thoracic vertebra and 2 cm. to the left of the vertebral column. The relation of the heart vector and leads is presented by the authors in geometrical terms. Instead of the equilateral triangle according to Einthoven they use an equilateral tetrahedron of which the frontal plane is the Einthoven triangle, placed vertically. By means of elementary geometry the relation of heart vector and leads can be expressed by an algebraic equation.

RESULTS

In the ideal case using these systems, the respective vectorcardiograms would be identical. This would hold true for normal as well as for ventricular premature beats. Actually, however, they are not identical. The degree of similarity is expressed as a figure, just as in our previous article; the figure 10 indicates perfect similarity.

The horizontal and frontal projections of the loop have been compared separately, and the

two figures thus obtained have been averaged. In Fig. 1 (A) and (B) two instances are given. In the first case (A) the similarity in B_1 and R_2 of the normal is better than that of the premature beats, while in (B) the reverse is the case. In Fig. 2 the figures expressing similarity of the normal beats

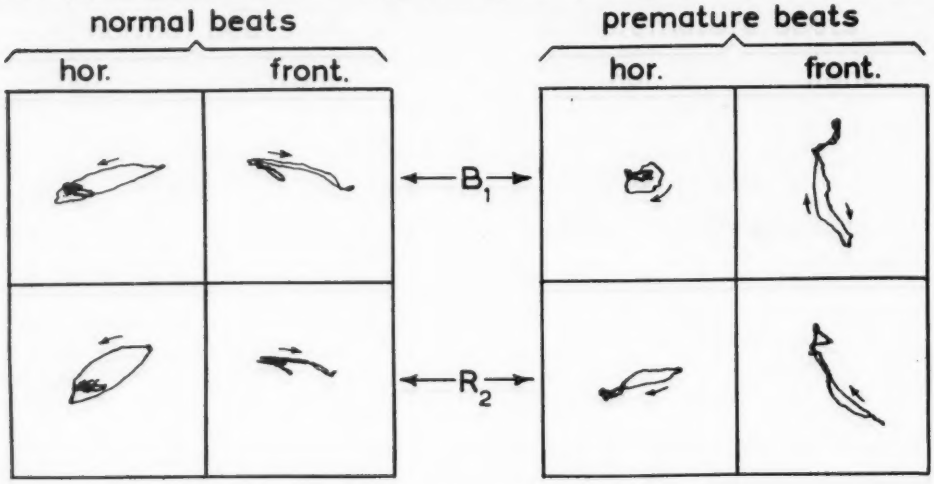

FIG. 1A.—Comparison of the respective normal and premature beats in the systems B_1 and R_2. The degree of correspondence of normal beats is greater than that of premature beats.

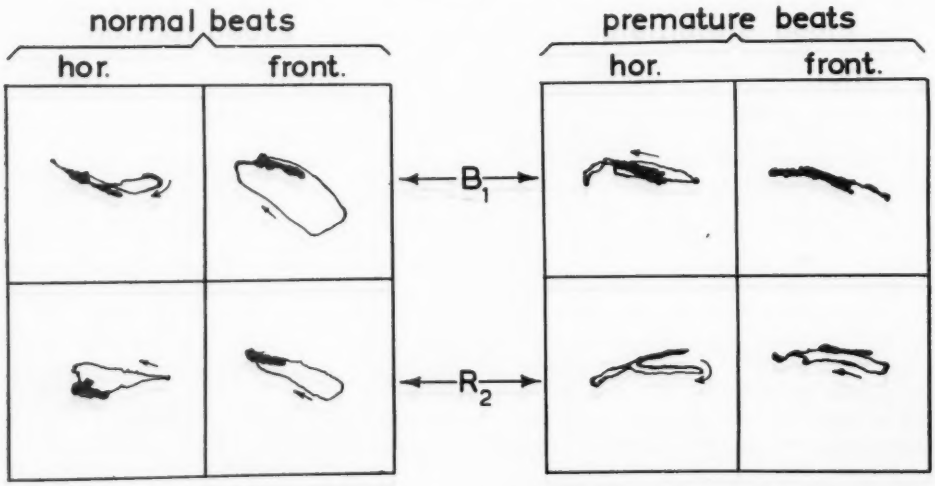

FIG. 1B.—Comparison of the respective normal and premature beats in the systems B_1 and R_2. The degree of correspondence of premature beats is greater than that of normal ones.

in B_1 and R_2 are plotted against those of the premature beats. In order to include also the system of the equilateral tetrahedron (W_4) in our considerations the averages of the three figures expressing the similarity of R_2 and B_1, R_2 and W_4, and of W_4 and B_1 are plotted in Fig. 3.

Conclusion. Fig. 2 and 3 show that there is no correlation between the figures for normal

beats and extrasystoles. With a clear correlation the dots would form a more or less straight line making an angle of about 45° with the axes. This would imply that a good correspondence of the normal beats, as a rule would be accompanied by a good correspondence of the premature beats, as in Cases 10 and 15 in Fig. 2. But the correlation is so slight, in fact, that there are cases in which a good correspondence of normal beats goes with a bad correspondence of the premature ones (8, 12, 3), while the reverse may also occur (7).

Discussion

The lack of an appreciable correlation indicates that the cause of non-identical vectorcardiograms in the different leads cannot be attributed to circumstances outside the heart, for these circumstances do not change at all when an extrasystole occurs. Nor can the size of the heart be of paramount importance. In the case of a large heart the excitation follows a course that is no longer insignificantly small with respect to the dimensions of the thorax. This will yield a lack of

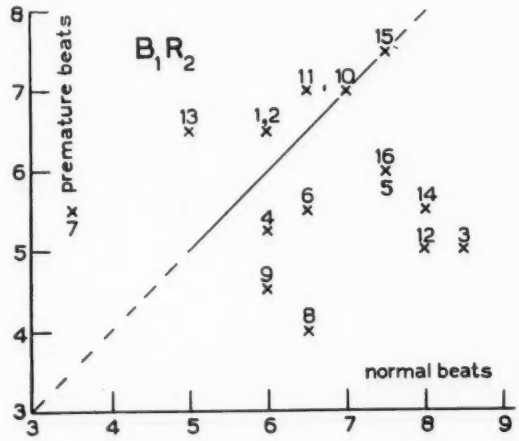

Fig. 2.—Similarity of the respective normal and premature beats in the systems B_1 and R_2.

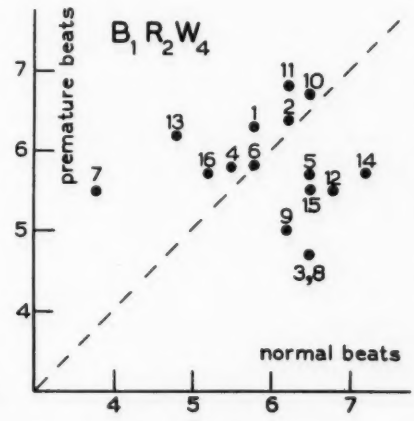

Fig. 3.—Similarity of the respective normal and premature beats in the systems B_1 R_2, R_2 W_4, and W_4 B_1.

correspondence in the different systems, not only of normal beats but also of extrasystoles. For this reason it cannot be expected that the discrepancy between the similarity of respective normal and premature beats can be explained by cardiac enlargement, which was excluded by fluoroscopy in the above-mentioned cases. So another explanation has to be looked for. It might be found in the occurrence of insulating local adipose tissue on the surface or in the neighbourhood of the myocardium. It is possible that this fatty tissue, because of its uneven distribution round the heart, affects the current field in the thorax differently in the case of a premature and a normal beat, as in each of these two cases the excitation proceeds differently through the heart.

In Fig. 2 it is remarkable that the similarity in B_1 and R_2 of normal beats is greater than that of premature ones. This might be accounted for by bearing in mind that in the phantom experiments an average position for the heart was assumed; with the eccentric origin of extrasystoles this assumption is not so valid. So it is probable that local factors can have a noticeable influence on the vectorcardiogram. It should be remembered, however, that this then also holds for the electrocardiogram.

Summary

In 16 subjects the degree of correspondence of the different vectorcardiographic lead systems (B_1, R_2, W_4) has been investigated in the case of both normal and premature beats. No correlation between the degree of correspondence of normal beats and that of premature beats was found. This makes it probable that the bad correspondence was due to local factors such as the uneven distribution of adipose tissue around the heart.

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Wilson, F. N., Johnston, F. D., and Kossman, C. E. (1947). *Amer. Heart J.*, **33**, 594.

MYOCARDIAL CHANGES OCCURRING IN POTASSIUM DEFICIENCY

BY

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Received June 11, 1954

Potassium has been recognized as essential for normal function of the myocardium since Ringer's studies in 1883. A deficiency of potassium may affect the heart in the human subject and result in a fall of the systolic blood pressure, in the appearance of abnormalities in the electrocardiogram (Bellet *et al.*, 1949; McAllen, 1951; Surawicz and Lepeschkin, 1953), and possibly in the development of acute heart failure (Goodof and MacBryde, 1944; Frenkel *et al.*, 1947; Gamble *et al.*, 1948).

Few pathological observations have been made on the hearts of patients with potassium deficiency, although much information is available from animal experiments. Follis *et al.* (1942) studied rats on a diet deficient in potassium and found constant changes in the myocardium and in the kidneys. After eight days on the diet, multiple small areas of muscle necrosis appeared. Concurrently, these areas were infiltrated first by polymorphonuclear leucocytes and later by mononuclear cells. These changes occurred in auricular and ventricular muscle. During the next few weeks the focal lesions increased in size and number, and by the sixth week proliferation of connective tissue had begun in the areas first affected. At the forty-seventh week, there was extensive fibrosis but occasional early type lesions were still appearing. The potassium content of the heart muscle of these animals was 35 per cent lower than normal controls. In the kidneys, there was dilatation of the convoluted tubules with necrosis of the lining epithelium. Other workers confirmed these findings and showed also that the longer the duration of the low potassium state the more extensive the cardiac damage, and further, that potassium chloride added to the drinking water prevented the development of the myocardial lesions (Darrow and Miller, 1942; Smith *et al.*, 1950; Peschel *et al.*, 1951; French, 1952). Similar changes have been found at autopsy in a few human subjects and these lesions have been attributed to potassium deficiency (Goodof and MacBryde, 1944; Roderiguez *et al.*, Cases 1 and 2, 1950; Perkins *et al.*, 1950; Luft *et al.*, Case 1, 1951; Keye, 1952). In half of these cases the evidence of potassium deficiency was clinical alone, and the duration of the condition was a few days only in all but two cases.

This report presents the clinical, biochemical, and necropsy findings in two well established cases of prolonged potassium deficiency. In each case extensive myocardial lesions were present.

CASE REPORTS

Case 1. A man, aged 41 years, had idiopathic steatorrhœa with muscular weakness of four months duration. When admitted to hospital on May 18, 1950, the patient was very weak in all limbs and unable to sit up. Clinical examination of the heart was normal. The blood pressure was 95/50. An X-ray of the heart and lungs revealed no abnormality. The hæmoglobin was 11·5 g. per 100 ml. and the red cells were 3,560,000 per c.mm. The Wassermann reaction was negative. Blood chemistry values per 100 ml. of serum were: sodium 295 mg., potassium 12·1 mg., chlorides (as sodium chloride) 620 mg., calcium 8·3 mg., phosphorus 1·9 mg. The electrocardiogram showed a flat T wave in the standard leads and a slight depression of the S–T segment with an inverted T wave in leads V3 and V5 (Fig. 1A). These changes disappeared in later tracings when the serum potassium was normal.

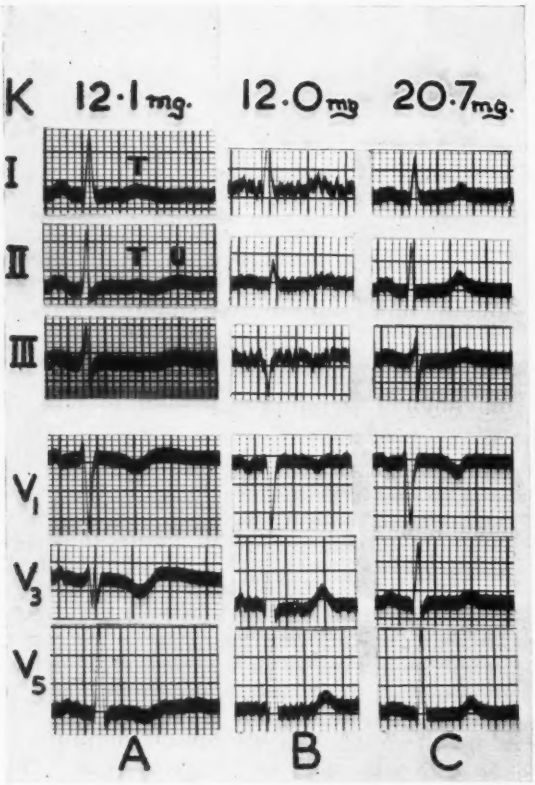

FIG. 1.—Case 1. (A) Tracings taken in 1950 when the serum potassium level was 12·1 mg. per 100 ml. The S–T segment is slightly depressed in leads V3 and V5, the T wave is low in the standard leads and inverted in leads V3 and V5. A small U wave is visible in several leads. (B) Tracings taken in 1953 when the serum potassium level was 12·0 mg. per 100 ml. The S–T segment is depressed in leads V3 and V5. (C) Tracings taken in 1953 at a time when the serum potassium was 20·7 mg. per 100 ml. Normal curves.

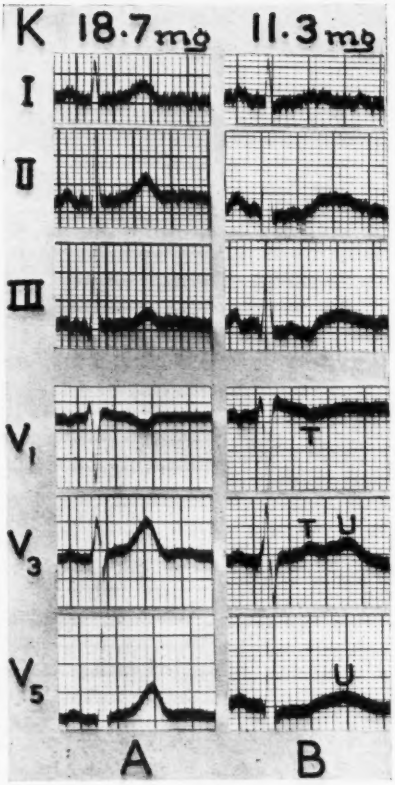

FIG. 2.—Case 2. Examples of the electrocardiogram before March, 1950. (A) Normal tracings when the level of serum potassium was normal. (B) Abnormal tracings when the level of serum potassium was low. In most leads the S–T segment is depressed, the T wave is flat or inverted, and the U wave is abnormally high and wide. (It was possible to correct these abnormalities within one hour by the administration of 7·5 g. of oral potassium chloride.)

Potassium chloride 10 g. daily was given orally for the first four days, and on this therapy the weakness lessened and the level of serum potassium became normal. Folic acid and a diet of low fat and high protein content produced general improvement. The blood pressure rose to 130/70. After five weeks, the patient was discharged home and he remained well with normal bowel action for the next two years.

Early in 1953, severe diarrhœa recurred and the patient was re-admitted to hospital on February 3, 1953. He was dehydrated, weak, and all peripheral reflexes were diminished. The heart sounds were normal and there were no murmurs. The blood pressure was 98/55. The hæmoglobin was: 12·1 g. per 100 ml. and the red cells were 4,400,000 per c.mm. Blood chemistry values per 100 ml. of serum were: sodium 272 mg., potassium 12·0 mg., calcium 9·6 mg., total proteins 3·2 g., albumin 2·1 g., and globulin 1·1 g.

He was given penicillin, aureomycin, folic acid, parenteral liver extract, blood transfusions, oral and intravenous saline, and oral potassium chloride 5 g. daily, but failed to improve. He was uncooperative,

and would only take a diet very low in protein. After two weeks, he developed œdema of sacrum and legs. At this time, the jugular venous pressure was not raised and the heart sounds were unchanged. A few days later light jaundice appeared with bile pigments in the urine. Liver function tests showed: serum bilirubin 3·9 mg. per 100 ml., alkaline phosphatase 50 King-Armstrong units per 100 ml., thymol turbidity 1 unit, thymol flocculation negative, and serum gold reaction negative. The serum potassium values remained low (11–14 mg. per 100 ml.). Even after increasing the oral potassium chloride dosage to 15 g. daily the serum potassium reached normal values on occasional days only. During the fourth and fifth weeks the œdema, jaundice, and diarrhœa persisted. He became drowsy, very weak, and died on March 10, 1953.

During this last admission the electrocardiographic changes were slight. When the serum potassium was low the S–T segment was depressed in leads V3 and V5 (Fig. 1B). A normal tracing was obtained when the serum potassium was within normal limits (Fig. 1C).

An electrolyte balance was carried out two weeks before death. This showed a retention of sodium and a markedly negative balance for potassium, the latter being attributable to an abnormal loss of potassium in the stools.

Necropsy (body weight, 55 kg.). The heart weighed 240 g. All valve orifices and cusps were normal. The myocardium was of normal thickness and no fibrosis was visible. Detailed dissection of the coronary artery system showed healthy vessels with no atheroma, narrowing, or occlusion. In the lungs a suppurative bronchiolitis was present. The liver on section showed a pattern of zonal pallor, and the bilary system was free from obstruction. The remaining organs showed no significant change.

Histology. In all parts of the myocardium there were foci showing loss of striation of the muscle fibres (Fig. 3), and sometimes vacuolation (Fig. 4). The nuclei of the myocardial fibres in these areas varied markedly in size, shape, and depth of staining. Small collections of monocytes and lymphocytes, and

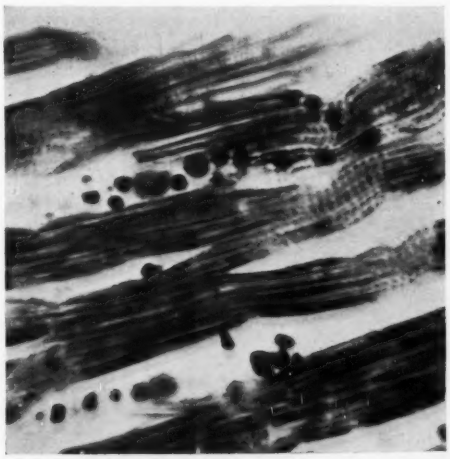

FIG. 3.—Case 1. Area of left ventricle showing transition from normal muscle fibres to muscle fibres with loss of cross striation. Heidenhain's stain (×380).

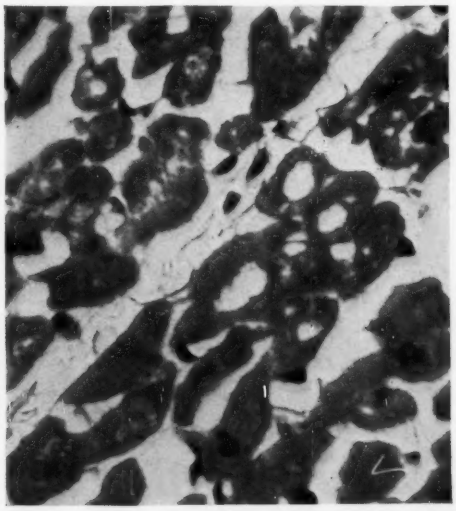

FIG. 4.—Case 1. Vacuolation of muscle fibres in right ventricle. H. and E. (×380). The vacuoles did not react to stains for fat or glycogen.

increased numbers of fibroblasts were seen in the interstitial tissue. Fibrous tissue frequently occurred as bands between muscle fibres (Fig. 5) and occasionally as small areas of muscle replacement (Fig. 6). All sections of the coronary arteries were free from abnormality. In the liver there was fatty change in the peripheral zones of the lobules. Sections of the small intestine showed a dense and extensive lymphocytic infiltration of the mucosal and submucosal layers. In the renal tubules some dilatation was present but no vacuolation or necrosis of the lining epithelium.

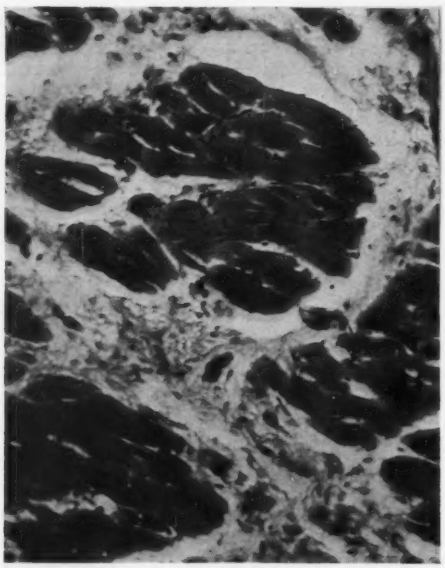

FIG. 5.—Case 1. Bands of fibrous tissue in right ventricle. H. and E. (×80).

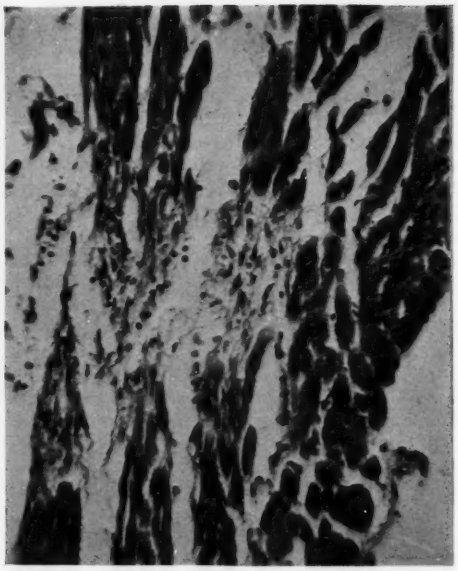

FIG. 6.—Case 1. Focus of fibrosis replacing muscle in left ventricle. There is a cell infiltrate consisting mainly of lymphocytes. H. and E. (×80).

Potassium Content of Heart Muscle. A piece of the left ventricle was chemically analysed and found to contain 15 mg. of potassium per 100 g. of wet tissue. This represents a greatly reduced content, the average normal value being a little over 300 mg. per 100 g. of wet tissue (Iseri *et al.*, 1952; Clarke and Mosher, 1952).

Case 2. A woman of 49, suffering from chronic ulcerative colitis, had attacks of marked muscular weakness due to potassium deficiency which began in 1948. Previously reported studies (Lubran and McAllen, Case 1, 1951) showed that this deficiency was dependent on a large potassium loss in the stools. On examination, the heart sounds were normal and there were no murmurs. The blood pressure was 110/70. The blood Wassermann and Kahn reactions were negative. An X-ray of the heart was normal in size and outline. The electrocardiogram showed a depressed S–T segment, an abnormally low or inverted T wave, and a large U wave when the serum potassium was low, but no abnormality when the serum potassium was normal (Fig. 2, and also figures previously presented, McAllen, Case 3, 1951).

During 1948 and 1949, the colitis fluctuated in degree and was mostly severe. A daily maintenance dose of 8–10 g. of potassium chloride was regularly required to prevent the attacks of muscular weakness recurring. Often this large daily dose only maintained the fasting serum potassium around a level of 12 mg. per 100 ml.

On March 3, 1950, the patient suddenly became unconscious and was admitted to hospital. There had been retrosternal pain for the previous twenty-four hours. Examination of the heart now revealed a soft apical systolic murmur and triple rhythm. The blood pressure was 100/70. No localizing signs were present in the central nervous system. A lumber puncture produced a clear fluid which was found to contain 72 mg. of protein per 100 ml. but was otherwise normal. Serum potassium was 11·0 mg. per 100 ml. The electrocardiogram (Fig. 7A) was quite unlike the tracings taken previously at a similar level of serum potassium (Fig. 2B) and showed changes considered to be those of a recent anterior myocardial infarct. The patient was thought to have had associated cerebral embolism. She regained consciousness after seven hours.

On March 8, the left femoral artery became suddenly occluded. An embolus was removed from the bifurcation of the left common iliac artery, but amputation of the leg became necessary. Subsequent

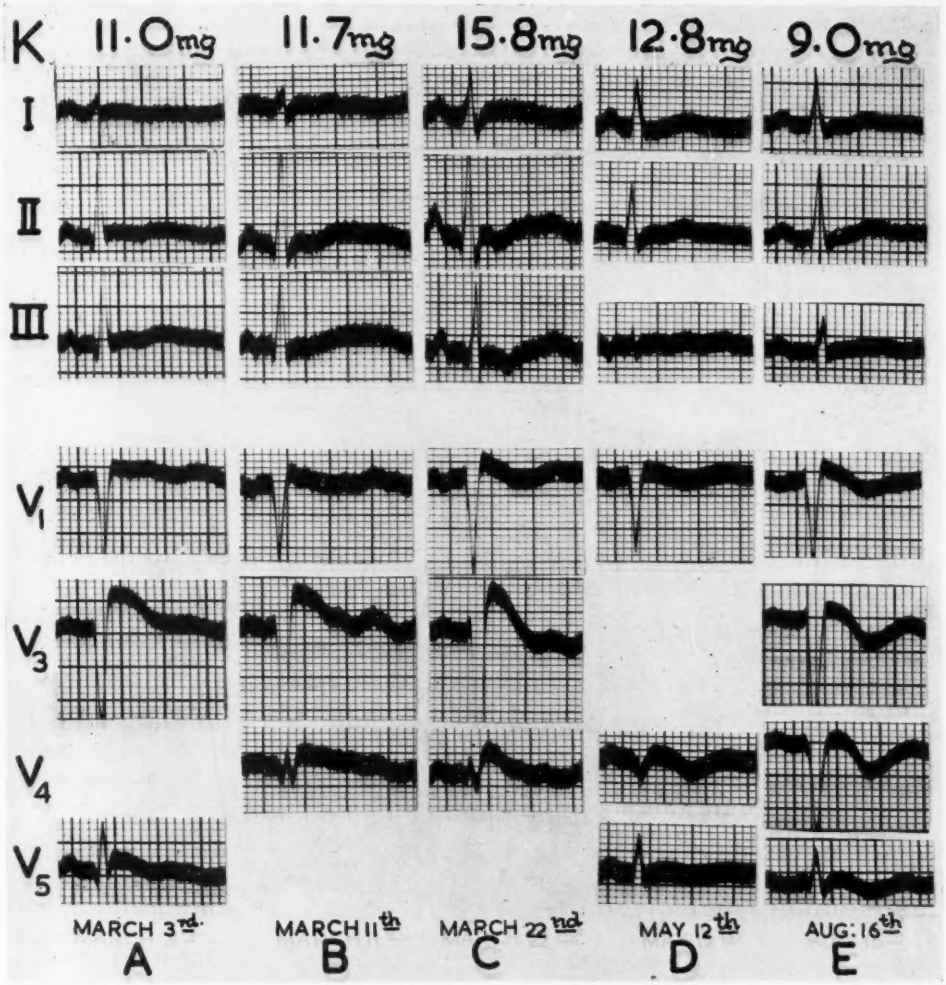

FIG. 7.—Case 2. Serial electrocardiograms taken during 1950 with simultaneous serum potassium levels. (A) March 3, the S–T segment is abnormally elevated in leads II, III, V3, and V5, the T wave is low in all leads, and the U wave is inconspicuous. (B) March 11, and (C) March 22. The tracings on both days are similar to those on March 3, and are little affected by the differences in the level of the serum potassium. A pathological Q wave is seen in lead V4. (D) May 12, and (E) August 16. The S–T segment is no longer elevated, the T wave has become inverted in leads V3 and V5, and the Q wave persists in lead V4. (Administration of 10 g. of oral potassium chloride at this time did not correct the abnormalities but increased the inversion of the T wave.)

electrocardiograms (Fig. 7B–E) showed serial changes in the S–T segment and T wave, together with pathological Q waves, typical of cardiac infarction. The patient was discharged home on July 22, 1950.

During 1951, there was a further severe exacerbation of diarrhœa. The patient would not attend hospital for some months and no potassium salts were taken. Eventually, bouts of muscular weakness returned and became incapacitating. At this time, a second attack of retrosternal pain occurred and one week later, October 25, 1951, the patient was re-admitted to hospital. On examination, there were no

abnormal signs in the cardiovascular system. The blood pressure was 140/90. In the electrocardiogram (Fig. 8A) the same abnormalities were seen as on discharge in July, 1950 (Fig. 7E). The serum potassium was 13·0 mg. per 100 ml. After seven days' treatment with potassium salts weakness disappeared.

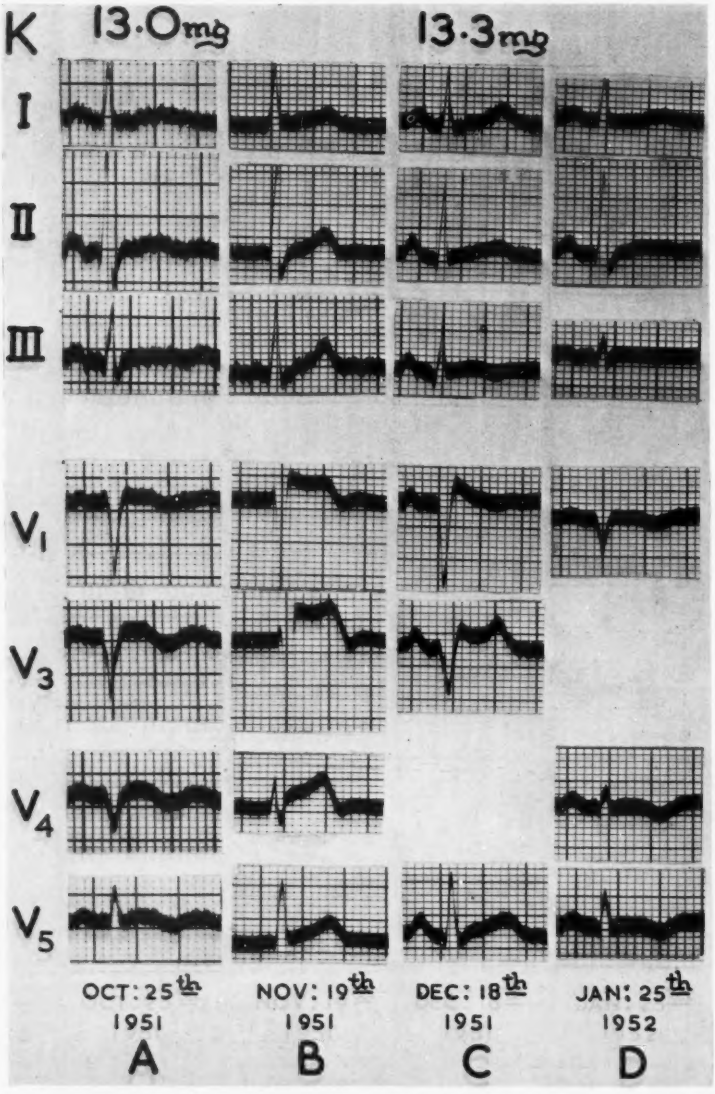

FIG. 8.—Case 2. Electrocardiograms taken during 1951 and 1952. (A) October 25, 1951. The abnormalities present are similar to those of August 16, 1950 (Fig. 7E). (B) November 19, 1951. In all leads there is an elevation of the S–T segment and an increase in voltage of the T wave. The rhythm is apparently nodal. (C) December 12, 1951, and (D) January 25, 1952. These tracings show gradual disappearance of the elevation of the S–T segment, and fall of the T wave to the previous low voltage or inversion. Sinus rhythm has returned.

On November 19, 1951, a third attack of severe lower sternal pain developed. Examination of the heart at this time did not reveal triple rhythm or any murmurs. The blood pressure was now 90/60. An electrocardiogram (Fig. 8B) showed a new elevation of the S–T segment in all leads indicating further damage to the myocardium. The pain disappeared after forty-eight hours. Subsequent tracings over the next two months (Fig. 8 C and D) showed a gradual disappearance of the recent changes but a persistence of the old abnormalities. The serum potassium level over this period was usually below normal.

On February 1, 1952, the patient suddenly developed a right hemiplegia and also occlusion of the right femoral artery. An embolus was shortly removed from the femoral artery but the patient died ten hours after operation.

Necropsy (body weight 50 kg.). The heart weighed 245 g. In the left ventricle (thickness up to 1·4 cm.) there was an area of fibrosis and thinning (2×2·5 cm.) involving the apex anteriorly and the adjacent part of the interventricular septum. A recent antemortem thrombus (1·5×1×1 cm.) was present on the endocardial surface of the fibrosed area. Appearances of the right ventricle and both auricles were normal. All valves were normal. Healthy and full-sized coronary ostia were present. Both coronary arteries and their branches were completely free from narrowing or occlusion, and showed only occasional, small, scarcely raised, flecks of atheroma. The smaller divisions of these arteries were dissected and found to be free from disease. In the aorta and other systemic arteries there was no atheroma. The colon showed the appearance of the late fibrous stage of chronic ulcerative colitis. The left kidney (weight 145 g.) had a capsule that stripped with difficulty and a finely granular surface. On section the pattern was normal. The right kidney was absent (nephrectomy for renal abscess in 1938). In the brain there was an embolus in the left middle cerebral artery.

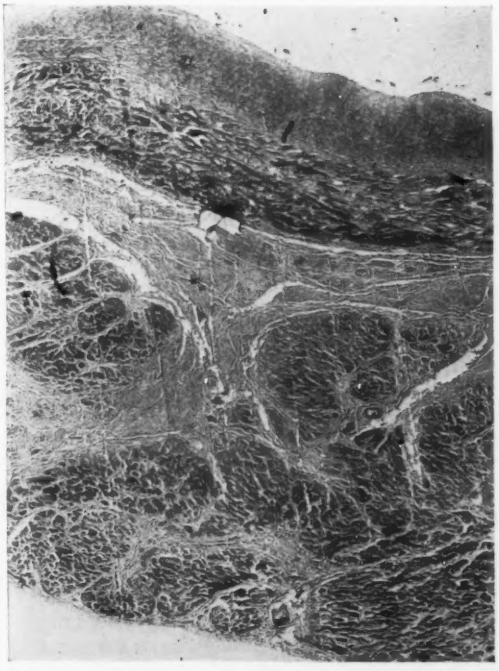

FIG. 9.—Case 2. Low-power view of a section through the scarred area at the apex of the left ventricle. Strands of fibrous tissue are seen throughout the whole thickness of the myocardium and are gathered into dense bands in its middle third. The endocardium is locally thickened by fibrosis. H. and E. (×20).

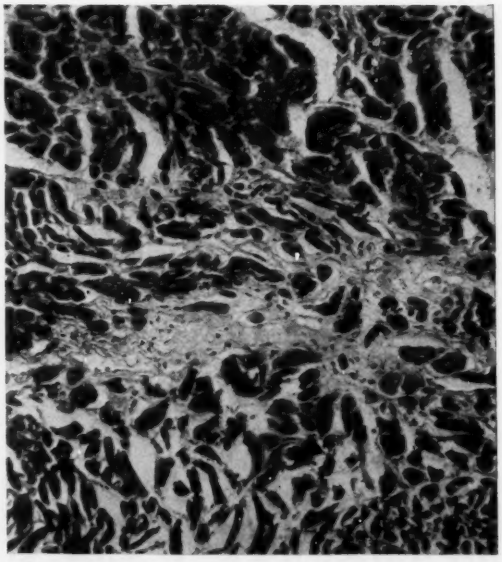

FIG. 10.—Case 2. Small focus of fibrosis in the myocardium of the left ventricle. H. and E. (×380).

Histology. The scarred area at the apex of the left ventricle showed bands of fibrous tissue of varying size running throughout the whole thickness of the myocardium (Fig. 9). Fibrosis was also seen in the remainder of the left ventricle, but mainly as multiple small foci unrelated to blood vessels (Fig. 10). Similar focal fibrosis was present in all parts of the right ventricle and both auricles. The fibroblasts between the muscle fibres were frequently increased in number and collected into groups. There were also occasional small collections of polymorphonuclear leucocytes between the muscle fibres. Examination of the coronary artery system showed only slight diffuse concentric fibrous endarteritis in the larger vessels. Sections of the kidney revealed healed chronic pyelonephritis. In the renal tubules, neither necrosis not vacuolation of the lining epithelium was observed.

Discussion

In the two cases described here, widespread myocardial fibrosis was present yet the coronary arteries were patent and free from disease. Myocardial fibrosis with normal coronary vessels has been reported in occasional cases of Friedreich's ataxia (Russell, 1946), familial cardiomegaly (Evans, 1949), pseudohypertrophic progressive muscular dystrophy (Weisenfeld and Messinger, 1952), scleroderma (Weiss *et al.*, 1943), chronic malnutrition (Gillanders, 1951; Higginson *et al.*, 1952), hæmochromatosis (Sheldon, 1935; Swan and Dewar, 1952), and in isolated cases of thyrotoxicosis (Weller *et al.*, 1932), syphilis (Warthin and Arbor, 1925), diphtheria (Burkhadt *et al.*, 1938), and rheumatic fever in the absence of damage to the valves (Wood, 1950). It may also be found in endocardial fibrosis when there is an extension of the process into the underlying muscle (Bedford and Konstam, 1946; Gray, 1951). None of these conditions was present in either of the cases recorded in this paper. Myocardial fibrosis has been attributed sometimes to a late stage of Fiedler's myocarditis (isolated myocarditis), but the description of this condition varies widely from case to case and it is doubtful if it exists as a specific ætiological entity (Saphir, 1941).

The occurrence of myocardial damage in potassium deficiency has been reported in a few cases (Goodof and MacBryde, 1944; Roderiguez *et al.*, 1950; Perkins *et al.*, 1950; Luft *et al.*, 1951; Keye, 1952). In most of these the lesions were acute, but in two (Perkins *et al.*; Roderiguez *et al.*, Case 2) a slight degree of myocardial fibrosis was also present.

In both the cases reported in the present paper a state of severe and prolonged potassium deficiency was fully established. A close parallel exists between the myocardial changes in these cases and those constantly found in experimental potassium deficiency. In Case 1, the cellular response and the necrotic appearances of the myocardial fibres are the same as those seen during the early weeks of experimental deficiency; and the fibrosis is similar in distribution and type to that found in later weeks. On chemical analysis, the potassium content of the heart muscle was greatly reduced, and this finding is a further important correlation with the animal experiments. In Case 2, the fibrosis was extensive and the cellular response slight, these being the same appearances observed in prolonged experimental deficiency. The low potassium state in this case continued over the greater part of four years and is one of the longest so far recorded.

Caution must always be applied when comparing the effects of animal experiments to human disease and particularly in potassium deficiency where the results vary with the species. Deficiency of potassium in rats (Follis *et al.*, 1942), mice (Liebow *et al.*, 1941), and swine (Thomas *et al.*, 1940), produces myocardial damage without paralysis of voluntary muscle; whereas in dogs, muscular weakness occurs without myocardial change (Smith *et al.*, 1950). However, in man it appears that both voluntary and cardiac muscle can be affected, and there seems little doubt that in the cases reported here the potassium deficiency was the direct cause of the myocardial damage.

A state of potassium deficiency in man is usually associated with other biochemical disturbances, but there is no evidence at present that imbalance of any other electrolyte is responsible for myocardial damage. Recent experimental work, however, has shown that if excessive sodium is administered to potassium deficient rats the resulting damage is more rapid and severe; conversely, if the sodium intake is restricted the myocardial damage is retarded (Cannon *et al.*, 1953). In Case 1, the sodium intake was large and there was evidence of sodium retention over the last three weeks of life. This event may have been a factor in the production of the acute changes found

in the myocardial fibres. In Case 2, on the other hand, there was an abnormal loss of sodium as well as potassium in the stools, and this may have enabled the heart to withstand the potassium deficiency for a long time.

A low protein state has also been found experimentally to accelerate the myocardial damage produced by potassium deficiency (Cannon *et al.*, 1952; French, 1952). In Case 1, a low protein state was present and may also have played a part in the production of the acute changes. In the experimental work on rats, the kidneys constantly showed dilatation of the convoluted tubules together with necrosis and vacuolation of the lining epithelium. Similar lesions have been described in two of the previously reported human cases (Perkins *et al.*, 1950; Keye, 1952). In Case 1, only slight dilatation of the tubules was found. In Case 2, the appearances were normal apart from focal healed chronic pyelonephritis.

The several episodes of cardiac pain in Case 2 remain unaccounted for. It is conceivable that from time to time the intracellular electrolyte disturbances were sufficiently severe to cause areas of myocardial necrosis. Such a conception would explain the episodes of chest pain, the coincident electrocardiographic changes indicating cardiac infarction, and the subsequent finding at autopsy of scarring visible to the naked eye. It is of interest that in the second case described by Roderiguez *et al.* a large area of myocardial softening was found at autopsy, but details of the cardiac symptoms are not given and no electrocardiogram is available. In Case 1, although there were multiple focal myocardial lesions, these apparently were not extensive enough to produce cardiac pain or permanent electrocardiographic changes. The electrocardiogram was affected only by changes in the level of the serum potassium, and this applied also to the cardiogram in Case 2 before the occurrence of chest pain.

In this paper, further evidence is produced to show that potassium deficiency in man may result in damage to the myocardium. If the deficiency is severe or prolonged the damage may be considerable. These findings indicate that a low potassium state should be corrected as quickly and completely as possible in order to avoid permanent cardiac injury; and further, that experiments on potassium deficiency in the human subject should be undertaken with caution.

Summary

Two cases of prolonged and severe potassium deficiency are described with particular reference to the cardiac findings before and after death.

In both cases, widespread myocardial fibrosis was present, yet the coronary artery system was patent and free from disease. In one, focal necrosis of the myocardium was also seen.

A close parallel can be drawn between the findings in these cases and those in potassium deficiency in experimental animals.

It is considered that the cardiac lesions were the direct result of potassium deficiency, and that such a deficiency should be corrected as quickly as possible if irreparable myocardial damage is to be avoided.

I wish to thank Dr. N. F. Coghill for permission to study his cases. I am indebted to Dr. A. C. Counsell for his great assistance with the pathology, to Dr. M. Lubran for advice on the biochemistry, and to Dr. Wallace Brigden for his helpful criticism of the paper. I also wish to thank Mr. D. A. Vinten for preparing the microphotographs.

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THE DISTINCTIVE ELECTROCARDIOGRAM OF CORONARY ARTERIOSPASM

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The value of the electrocardiogram in the diagnosis of cardiac pain needs no emphasis. Experience has confirmed the unreliability of the patient's description of his pain as a guide to its cause. Thus, when the progress of over 300 patients in whom chest pain was subjectively characteristic of cardiac pain, was watched over many years, the pain proved to have a dyspeptic or some other non-cardiac source, and successive electrocardiograms remained normal (Evans, 1952). The history of the illness in such patients differed in no particular way from that obtained from a patient where the cardiogram proved the presence of cardiac infarction. Thus, the pain, usually in the centre of the chest, was described as gripping or tightness, often radiating into the arms or the jaw, and readily brought on by exertion, and as a rule yielding as quickly to rest. It is also known that physical signs are sparse in the many patients in whom the myocardial injury initiating the pain is not severe enough to prevent them from being ambulatory or even from following their customary occupation. In more than four-fifths of such cases reliance has to be placed on the electrocardiogram as the only means of telling the cause of the symptoms. A characteristically abnormal tracing confirms the presence of cardiac pain, but views on the meaning of a normal tracing need affirming. Whether a strictly normal electrocardiogram can exclude cardiac infarction as the cause of chest pain is a question that calls for an answer, and this paper is meant to contribute to a solution of the problem.

The bipolar CR chest leads have been used deliberately instead of V leads because of their superiority in the investigation of the lesser injuries in the heart following coronary arterial disease; especially does this apply to CR7 where the T wave in health is upright whereas in V7 it is low, sometimes flat, and occasionally inverted.

Scope of the Inquiry

During a period when 1000 consecutive patients with cardiac infarction were examined, 322 other patients were found with like chest pain, but in whom the electrocardiogram seemed normal and where a non-cardiac, and usually dyspeptic, cause was operating. To this latter group 48 such cases have been added since the series with cardiac infarction was completed so that the number with normal tracings is now 370. The progress of all 1370 patients has been watched at intervals of less than two years in order to observe their longevity and the changes that might take place in successive electrocardiograms. In the first group of 1000 patients tracings that might have returned to normal were sought, while in the second group of 370 patients, each with an apparently physiological electrocardiogram, a watch was kept for abnormal changes that might appear subsequently and so would give proof that coronary arterial disease had caused the pain from the start. The period of observation has extended over two years in 829 patients, over four years in 482, over six years in 238, over eight years in 65, and over ten years in 47 patients.

The Electrocardiogram customarily found in Cardiac Pain

The design of the electrocardiogram in the series of patients with cardiac infarction conformed to one of six types, and although these corresponded roughly with the location of the infarct in the isolated examples examined at necropsy, it is known that the electrocardiographic pattern cannot define precisely the exact limits of the infarct. There are a number of reasons for this. First, there is often a natural variation in the course of the affected artery. Secondly, the efficiency of the collateral circulation adjoining the infarcted area is inconstant. Thirdly, the position of the heart varies from its orthodox lie in the chest in different patients. Again, the site of the infarct and its nearness to the base or the apex of the heart affects the electrocardiogram, while the presence of healthy myocardium between the infarct and the electrode will alter its pattern. Lastly, the presence of more than a single area of infarction, old or new, disturbs the tracing. A number of investigators (Parkinson and Bedford, 1928; Whitten, 1930; Barnes and Hall, 1932; Barnes, 1934; Barnes, 1935; Lyon, 1938; Martensen, 1942; Myers *et al.*, 1948*a*, 1948*b*, 1949*a*, 1949*b*, and 1949*c*) have found a measure of agreement when correlating the electrocardiographic with the pathological findings, but since a strict correlation is often wanting, and since the location of most infarcts has no direct influence on prognosis, it is seldom wise to dogmatize on the place of the infarct. Instead, a better custom is to adopt the electrocardiographic classification, and the characteristic patterns for salient infarction are shown in Fig. 1 and for restricted infarction in Fig. 2; the incidence of each kind is shown in Tables I and II.

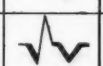
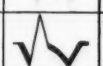
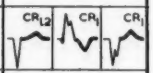
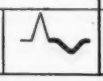
LEADS	ANTERIOR INFARCTION	LATERAL INFARCTION	POSTERO-INFERIOR (LATERAL) INFARCTION	POSTERO-INFERIOR (MEDIAL) INFARCTION	SEPTAL INFARCTION
I			—	—	–
II	—	—	—	–	–
III	—				–
III_R	—				–
$CR_{1,2}$	—	—	—	—	
CR_4		—	—	—	–
CR_7	—			— 	–

FIG. 1.—Diagrammatic representation of the electrocardiogram in *salient* cardiac infarction according to its situation. Q waves may be added in the anterior and lateral varieties.

The Normal Electrocardiogram in relation to Cardiac Pain

There were 24 instances where the electrocardiogram had been regarded as normal one time and was abnormal another time conforming to the kind found in cardiac infarction. When, however, the tracings in these cases were re-examined in the light of more recent experience of the lesser electrocardiographic changes in cardiac pain (Evans and McRae, 1952) the first opinion on their normality was rescinded in15. The changes that came to light in these cases following this more careful scrutiny included S–T depression, especially in IIIR, in six, low T wave in lead I

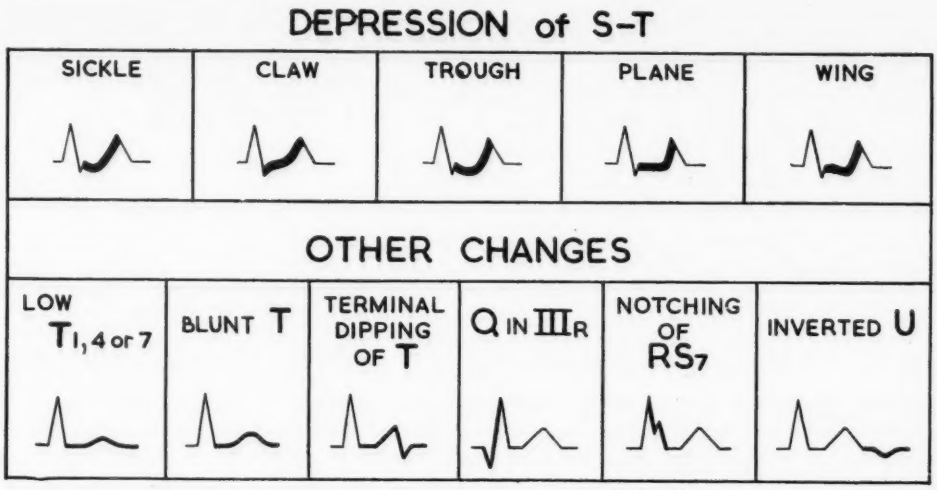


FIG. 2.—Diagrammatic representation of the lesser electrocardiographic changes in *restricted* cardiac infarction.

TABLE I

DISTRIBUTION OF THE INFARCT AND THE MORTALITY RATE AMONG 1000 CONSECUTIVE PATIENTS WITH CARDIAC INFARCTION

Distribution of the infarct		No. of patients	Deaths	
			Number	Mortality rate
Salient	Anterior	234	39	17
	Lateral	126	28	22
	Postero-inferior (lateral)	130	27	20
	Postero-inferior (medial)	132	24	18
	Septal	50	7	14
Restricted		328	60	19
Total		1000	185	19

and in CR4 or CR7 in three, the appearance of a significant Q wave in IIIR in three, a blunt T wave in CR4 in one, splintering of the RS in CR7 in one, and an inverted U wave in one.

There were left, therefore, nine electrocardiograms in patients with cardiac pain which one time showed no departure from the design at present accepted as belonging to a healthy subject, but another time showed the characteristic changes found in cardiac infarction (Table III). The number is very small (9 out of 1004) and this fact alone emphasizes the hesitancy with which a diagnosis of cardiac pain should be applied to a patient where the electrocardiogram fails to support it. Small as the number is, however, it calls for a close search for any special clinical or cardiographic features that might help in the readier recognition of patients in this group.

Eight of the patients were men and there was one woman. Their ages varied from 44 to 67 years and the average age was 52. The site and distribution of the pain was in no way distinctive, so that it was retrosternal in all, spreading into the left arm in four and into both arms in three.

TABLE II

THE INCIDENCE OF THE LESSER ELECTROCARDIOGRAPHIC CHANGES AND THE MORTALITY RATE IN 328 PATIENTS WITH RESTRICTED CARDIAC INFARCTION

Cardiographic sign	No. of patients	Death as sequel to cardiac infarction
Depression of S–T segment	206	35
Low T wave	86	23
Blunt T wave	8	2
Terminal dipping of T wave	5	0
Q developing in IIIR	14	0
Notching of RS segment in CR7	4	0
Inversion of U wave	5	0

TABLE III

THE INCIDENCE OF A NORMAL ELECTROCARDIOGRAM AMONG PATIENTS WITH CHEST PAIN CLINICALLY CHARACTERISTIC OF CARDIAC PAIN

Patients judged to have cardiac infarction (1000)		Patients with cardiac-like pain (370)	
Cardiogram remaining abnormal	Cardiogram returning to normal	Cardiogram remaining normal	Cardiogram initially normal, becoming abnormal
995	5	366	4 *

* These four cases were regarded at first as having cardiac-like pain on the grounds that their electrocardiograms were strictly normal.

Similarly, the character of the pain did not vary from that met with in patients with cardiac infarction, save that the pain seemed more liable to recur at night when it was often intense, lasting an hour or so, but without inducing a state of severe shock. On occasion also the relief of pain that followed exertion was not so instantaneous on resting as is usual in patients with pain from obstructive coronary arterial disease. In none of the nine patients was there hypertension, triple heart rhythm, cardiac enlargement, or pulmonary congestion; indeed, they showed no abnormal signs on clinical and radiological examination of the heart.

In four of the nine cases the normal cardiogram was the initial tracing and in five it was the subsequent one. When the patients were watched after they had shown the abnormal tracing it recovered completely in eight while in one the R wave remained absent in CR1 although the T wave had recovered in all leads.

Among the 1000 patients with cardiac infarction there were 234 who showed a depression or inversion of the T wave in lead I and inversion of the T in CR4, and these changes were accepted as meaning that the myocardial injury was situated for the most part in the anterior wall of the left ventricle (Table I). When the CR1 cardiogram was examined in these patients they were separated into two main groups (Table IV).

In the first group there were 140 patients in whom CR1 was a normal lead. During the time when the progress of these patients was watched there were 28 deaths. In no single instance did the electrocardiogram resume a strictly normal pattern.

In the second group of 94 patients some abnormality was present in CR1 and according to the kind of deformity, these patients were divided into four classes.

In 44 a significant Q wave was the only abnormal finding in CR1 and in none of these did the cardiogram recover; during the period of observation there were seven deaths.

Similarly, among the 26 patients where the CR1 lead showed inversion of the T wave as well

TABLE IV

THE PROGRESS OF ELECTROCARDIOGRAPHIC CHANGES IN 234 PATIENTS WITH DEPRESSION OR INVERSION OF THE T WAVE IN LEAD I AND INVERSION OF THE T IN CR4 IN RELATION TO FINDINGS IN THE RIGHT PECTORAL CARDIOGRAM (CR1)

State of the CR1 cardiogram		No. of patients	Patients showing complete recovery of the whole cardiogram	Deaths
Normal (140)		140	0	28
Abnormal (94)	Deep Q wave	44	0	7
	Q wave present and T wave inverted	26	0	2
	T wave inversion associated with changes in the general electrocardiogram	14	0	1
	Inversion of T wave only	10	8	0

as a Q wave, in none did the electrocardiogram recover completely. In one patient, however, a previous cardiogram had proved to be a normal tracing at a time when chest pain on effort was a symptom, but following the appearance of a Q wave in CR1 and CR2 in addition to inversion of the T wave in these leads and in I and CR4, a significant Q wave remained in CR1 and CR2 although the T waves had recovered (Fig. 3).

In a third group there were 14 patients where CR1 showed inversion of the T wave together with slight changes in the general cardiogram. These changes consisted of depression of the S–T segment in nine, a significant Q wave in leads I, CR4, or CR7 in three, a low T wave in leads I and CR7 in one, and an inverted U wave in one; such blemishes indicated injury to the lateral and/or postero-inferior portions of the left ventricle in addition to the anterior wall. In none of the 14 patients did the electrocardiogram recover completely during the period of observation when one died.

The fourth group held ten patients and in these, inversion of the T wave was the only deformity in the CR1 cardiogram. The electrocardiogram recovered in its entirety in eight out of the ten patients (Fig. 4 to 9). Even in the remaining two cases it had recovered at a subsequent examination except for a Q wave in CR1 in one (Fig. 10) and notching of the RS stem in lead CR7 in the other (Fig. 11). Thus, when inversion of the T wave in CR1 and CR4 was accompanied by significant Q waves or other lesser changes elsewhere in the tracing the cardiogram did not recover completely. Further, when T wave inversion in CR4 was not accompanied by T inversion in CR1 the cardiogram also failed to recover even in the absence of significant Q waves or depression of the S–T segment. Such results show that here is a distinctive electrocardiogram which possesses a remarkable facility to right itself even though at one time its deformity is so patent as to suggest an extensive myocardial injury. It is here proposed that this distinctive tracing in a patient subject to cardiac pain should be named the *mutable electrocardiogram.*

THE DESIGN OF THE MUTABLE ELECTROCARDIOGRAM

All ten patients whose electrocardiograms with two exceptions recovered wholly showed a common pattern. Thus, the T wave was inverted in chest leads CR1 to CR4 and was sometimes flat or inverted in the left ventricular leads as far as CR7; the T was inverted in lead I and occasionally in lead II as well, and it often lost height in IIIR. An abnormal Q wave was always absent in every lead, nor were there any changes customarily found in salient or restricted infarction graphically represented in Fig. 1 and 2. This distinctive electrocardiogram bears no resemblance to the one described for coronary insufficiency by Buchner *et al.* (1935) and by Master *et al.* (1941), in that depression of the S–T segment, regarded here as meaning restricted cardiac infarction, was not a feature of any of the cases.

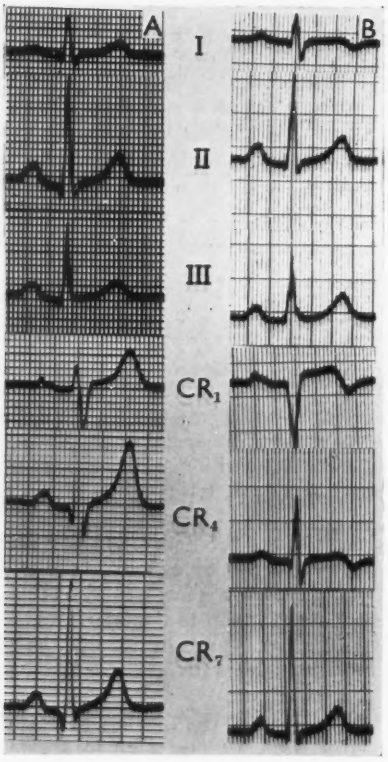


FIG. 3.—One-time normal electrocardiogram in cardiac pain. The tracing (A), recorded in a patient liable to chest pain on effort during the two previous weeks, is normal. (B) was taken a fortnight later and shows inversion of T wave in leads I, CR1, and CR4 as well as a deep Q wave in CR1. Subsequently the T waves recovered, but the significant Q wave remained in leads CR1 and CR2.

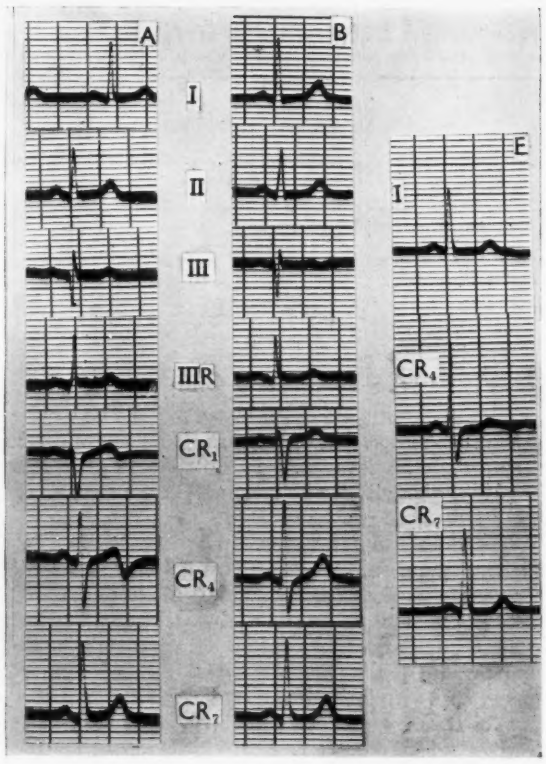


FIG. 4.—*Coronary arteriospasm.* In (A) the T wave is low in I, inverted in CR4, and shows terminal dipping in CR1. (B) recorded four months later is a strictly normal tracing; the exercise electrocardiogram (E) is abnormal.

The importance of *terminal dipping of the T wave* has already received emphasis (Evans and McRae, 1952) for it proved as useful as frank inversion of the T wave in the recognition of a myocardial injury from coronary arterial disease. This change in CR1 was tested to see whether its presence might indicate a special susceptibility to recover. This terminal dipping of the T in CR1 appeared in 5 of the 14 cases where lesser changes in the general tracing occurred in company with the features which characterize the mutable cardiogram; none of these tracings recovered completely. Again, the dipping T wave was present in 3 of the 9 cases where the cardiogram was onetime strictly normal, so that the sign denotes the early age of the myocardial injury, and its presence or its absence does not predict the reversibility or permanence of any abnormal tracing so that in this respect it appears to have the same significance as frank inversion of the T wave.

The effect of *exercise* on the mutable electrocardiogram was sought in the nine patients that exhibited it; the strictly normal tracing became temporarily deformed following strenuous exercise

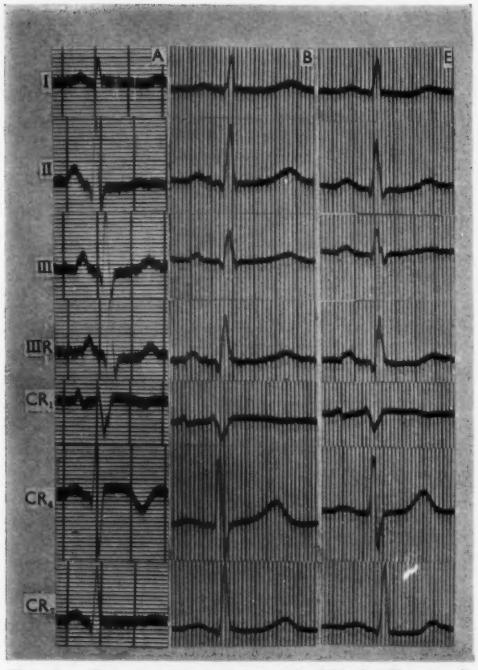


FIG. 5.—*Coronary arteriospasm.* In (A) the T wave is flat in leads I and CR7, low in lead II, and inverted in leads CR1 and CR4. (B) Recorded four years later is a strictly normal tracing; the exercise cardiogram (E) is abnormal.

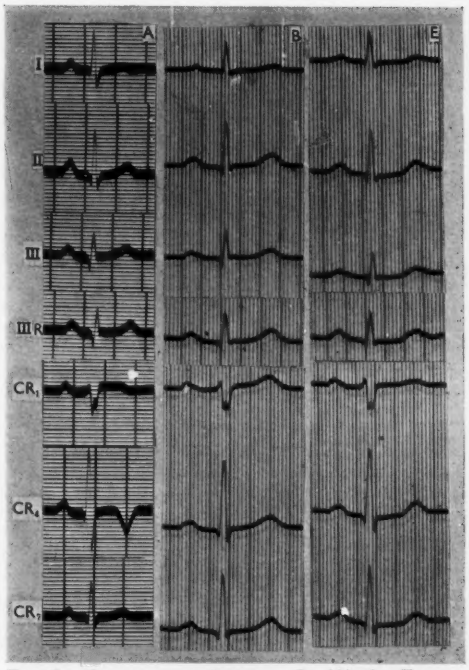


FIG. 6.—*Coronary arteriospasm.* In (A) the T wave shows terminal dipping in CR1, inversion in leads I and CR4, and is low in CR7. (B) Recorded three years later is a strictly normal tracing; the exercise cardiogram (E) is slightly abnormal.

in eight of the nine cases and regained its normal form within ten minutes of discontinuing the exercise. In most of the cases some months had elapsed since a severe paroxysm of pain had overtaken them, although most of them were experiencing periodic episodes of chest discomfort on exertion. In the remaining patient although an exercise electrocardiogram had once showed changes when the resting tracing was normal, a second test carried out when severe chest pain had been absent for over a year failed to produce any blemish in the tracing. It appears, therefore, that the fully recovered mutable cardiogram yields a positive test if this is carried out within six months, but if a longer period has elapsed, provided no strong attacks of pain have visited the patient, strenuous physical exercise may fail to induce a pathological change in the cardiogram even though chest discomfort on walking quickly has continued as a symptom.

THE SIGNIFICANCE OF THE MUTABLE ELECTROCARDIOGRAM

A watch over the progress of patients showing distinctive changes identified with this labile electrocardiogram has established the benignity of the lesion. Over many years in spite of the patients' liability to recurrent attacks of cardiac pain either following effort or while at rest, none died, and with two exceptions where the residual changes were slight, the electrocardiogram recovered completely within a few months of experiencing a severe episode of pain and showed no permanent changes due to frank cardiac infarction.

The characteristic deformity in the tracing indicates a diffuse and intense cardiac ischæmia from interruption of the blood flow in the left coronary artery. The wide distribution of the T wave

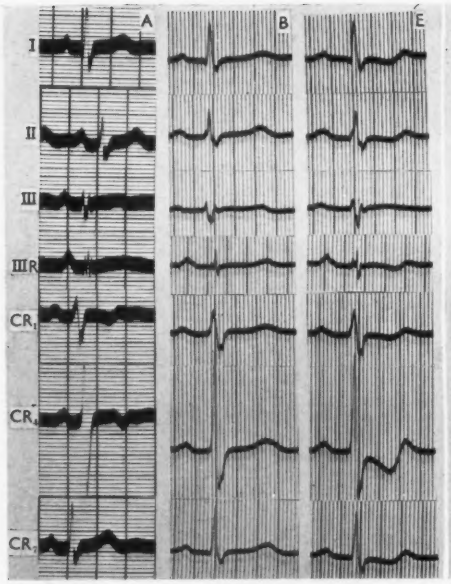


FIG. 7.—*Coronary arteriospasm.* In (A) the T wave is inverted in CR1 and CR4. The tracing (B) recorded a year later is within normal limits; the exercise cardiogram (E) is abnormal.

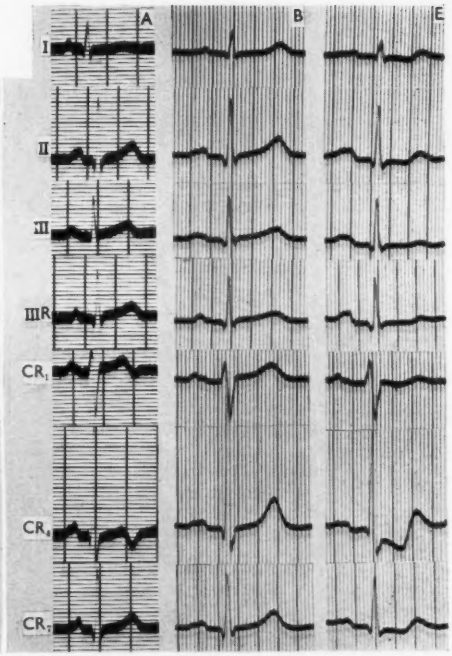


FIG. 8.—*Coronary arteriospasm.* In (A) the T wave is low in lead I, inverted in CR4, and shows terminal dipping in CR1; (B) recorded three years later is a strictly normal tracing; the exercise cardiogram (E) is abnormal.

inversion reaching station CR1 on the right and often as far as CR7 on the left suggests that the artery is involved near its source. Such interruption is short-lived and it does not last long enough to cause death of the patient nor any part of the heart muscle. In time, usually within three to six months and sometimes much sooner, the bruised muscle regains its normal state even if lesser episodes of pain recur in the meantime. This temporary interruption of the coronary blood stream appears to be explained by a spasm of an artery unaffected by material atherosclerosis. Other examples within one's experience appear to exhibit the same mechanism in the presence of coronary arterial disease, when the electrocardiogram has recovered to a remarkable degree, although not wholly (Fig. 12), and in such instances the myocardial injury, restricted to a small area, persists; naturally such a condition cannot claim the good prognosis which characterizes the special group where the recovered cardiogram shows no trace of blemish.

The effect of ingestion of *trinitrin* was not tried in the earlier cases when the electrocardiogram exhibited conspicuous inversion of the T wave because previous experience (Evans and Hoyle, 1933) had failed to give information of practical value from this test. When trinitrin, however, was prescribed while the electrocardiogram was showing a return to a normal pattern, the depressed T wave gained significantly in height (Fig. 13). This reaction also suggests that the T wave deformity in the mutable cardiogram is the outcome of cardiac ischæmia following temporary coronary arteriospasm rather than cardiac infarction from permanent coronary arterial occlusion.

Having regard to the mechanism inducing the cardiac ischæmia and the selective area of its distribution, the actual site of the spasm is in the left coronary artery distal to its circumflex branch

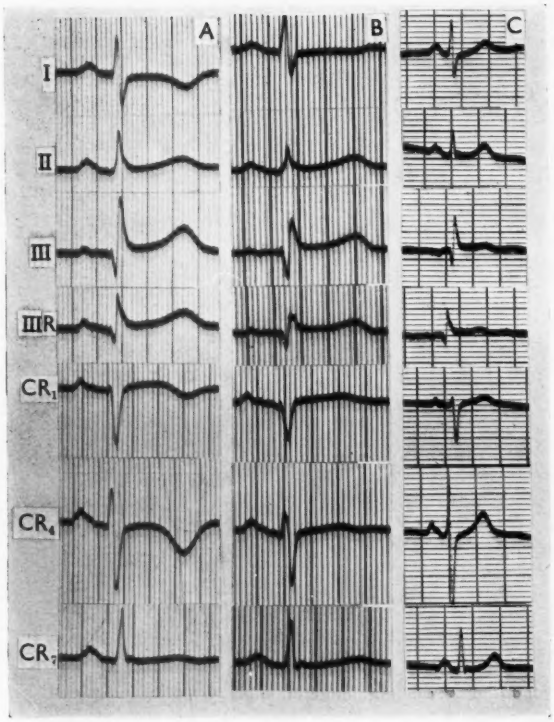


FIG. 9.—*Coronary arteriospasm.* In (A) the T wave is inverted in leads I, CR1, and CR4, and is low in CR7. The changes are slight in (B) recorded four months later, and are absent in (C) recorded two months later.

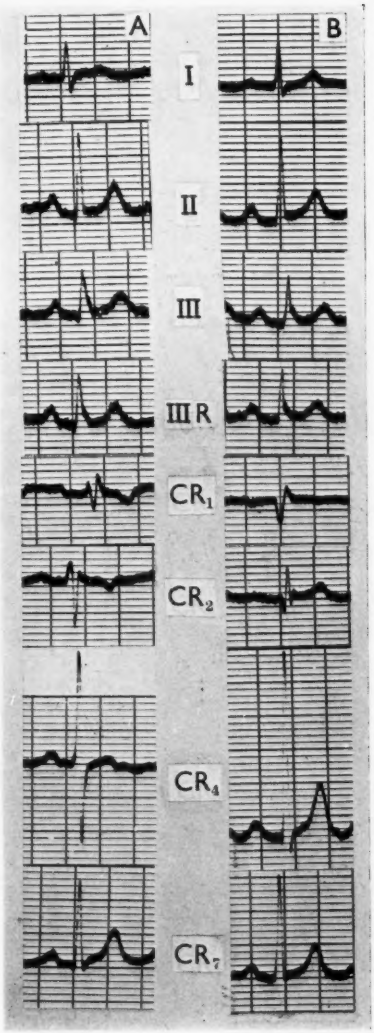


FIG. 10.—*Coronary arteriospasm.* In (A) the T wave is low in lead I and inverted in leads CR1, CR2, and CR4. The tracing (B) recorded two years later remains normal except for the presence of a Q wave in leads CR1 and CR2.

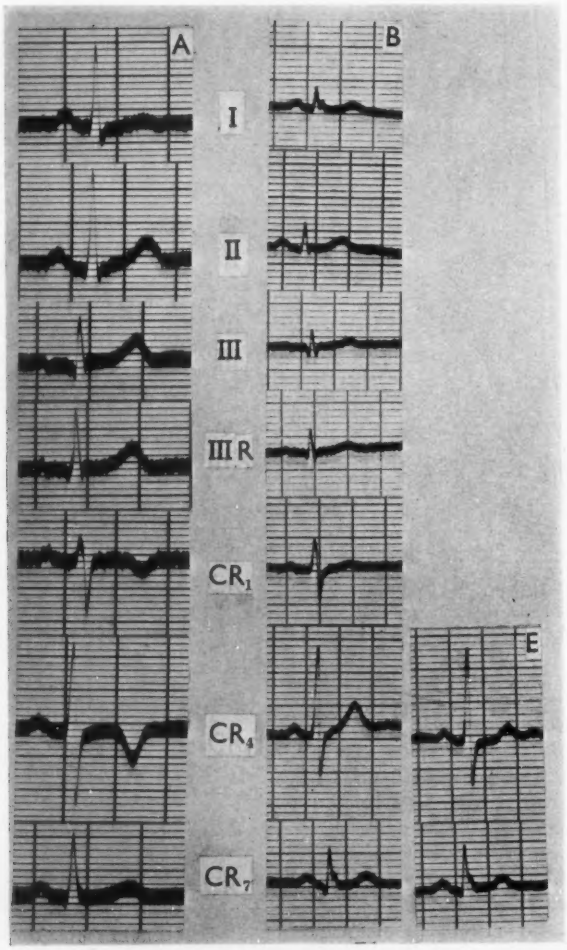


FIG. 11.—*Coronary arteriospasm.* In (A) the T wave is low in leads I and CR7 and inverted in CR1 and CR4. (B) recorded five months later is normal except for notching of the RS segment in CR7; the exercise cardiogram (E) shows no added abnormality.

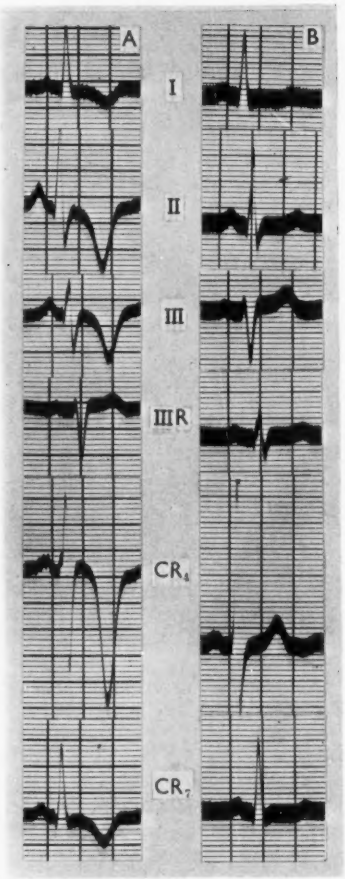


FIG. 12.—*Cardiac infarction.* In (A) the T wave is deeply inverted in leads I, II, III, CR4, and CR7. (B) recorded a year later shows remarkable recovery of the T waves which are low only in leads I, II, and CR7

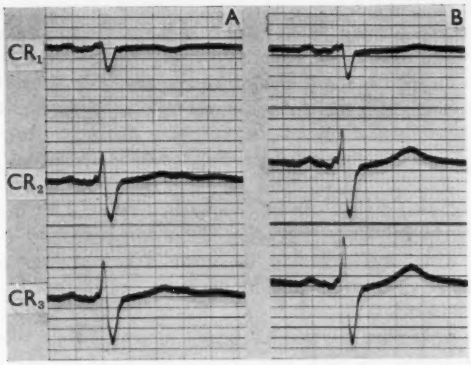


FIG. 13.—*Coronary arteriospasm.* An inverted T wave in CR1 and a low T in CR2 and CR3 in (A) from a patient showing the mutable electrocardiogram are upright in (B) recorded four minutes after chewing 1/25 gr. (2·6 mg.) of glyceryl trinitrate.

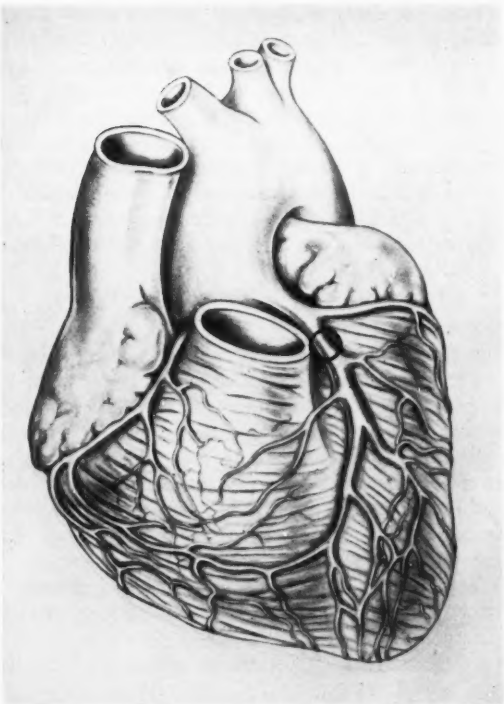


FIG. 14.—*Distribution of the left coronary artery.* The site of the arteriospasm which gives rise to the mutable cardiogram is indicated by a circle and is about 1 cm. proximal to the seat of election for atheromatous obstruction and thrombosis, and lies between the circumflex and the left marginal branches of the left coronary artery.

and proximal to the left marginal branch unless this takes origin from the left circumflex (Fig. 14). No other part of the coronary circulation has been found to be so susceptible to such abrupt and temporary closure for no example of complete recovery of an electrocardiogram has been met with among patients in whom the tracing allocated the injury to either the lateral or postero-inferior portions of the left ventricle. This distinctive segment of the coronary circulation possessing a special aptitude to spasm might be named the *coronary floodgate* for it can suddenly close and interrupt the blood supply to a large area of the heart and as readily it can open and re-establish the circulation.

It was late in the investigation that special attention was paid to the possible existence in the same patient of a like-spasm in situations other than the coronary circulation. Two possible examples of this were met with, one involving the retinal artery and the other the transverse colon, but as such episodes might have been fortuitous, they do not in the meantime allow one to draw firm conclusions from this association.

East and Oram (1948) published a valuable paper in which they recorded 34 cases of cardiac pain where a remarkable degree of recovery of the deformed T wave had taken place. They described 10 of these in detail and showed the electrocardiograms in nine. A right pectoral lead, however, was only available in one patient (their Case 3) and the tracing in this instance recovered completely except that the T wave in V1 remained slightly inverted; this demonstrates the inferiority of lead V1 with its tendency to show an inverted T in health, compared with CR1 in the investigation of these cases. In the bipolar lead, should deformity of the T wave remain, it would suggest that complete recovery of the ischæmic electrocardiogram had not taken place, although in the patients described here the deformity in the CR1 tracing usually disappeared earlier than the abnormality in CR4. Complete recovery of the electrocardiogram also took place in two other patients in East and Oram's series (their Cases 2 and 7), but in neither was the right pectoral lead recorded. In their remaining six cases recovery of the tracing was only partial and signs remained that indicated a residual myocardial injury. They, too, considered that spasm of the coronary artery had caused the temporary electrocardiographic changes. Thompson (1952) published three cases of cardiac pain to illustrate favourable results from treatment with anticoagulants. One of his patients (Case 2) showed a tracing identical in pattern with the mutable electrocardiogram described here; the tracing returned to normal and remained so during a period of three years when the patient had also kept free from symptoms.

Conclusion

Doubt has remained on the true significance of a strictly normal electrocardiogram in a patient in whom the diagnosis of cardiac pain is suspected. The time is not long past when a normal tracing in a patient whose pain apparently was caused by cardiac infarction, occasioned no surprise, but since the lesser electrocardiographic changes identified with coronary arterial disease have gained more general recognition the incidence of a normal cardiogram in such patients has decreased.

The question whether the electrocardiogram of cardiac infarction is ever normal still needs to be answered. The present investigation supports the view that it is never strictly normal provided the tracing has been a competent one, and provided the mutable electrocardiogram described here and signifying coronary angiospasm is recognized. When cardiac pain arises from such spasm the tracing becomes grossly abnormal from the ensuing cardiac ischæmia, always preserving a consistent pattern, and thereafter gradually returning to assume its previous normal design even though light attacks of cardiac pain continue to recur.

The mutable electrocardiogram is characterized by inversion of the T wave in chest leads CR1 to CR4 and often beyond this as far as station CR7; early on, the deformity may be confined to the terminal portion of the T wave which may dip sharply below the iso-electric level. The T wave is usually inverted in lead I as well Signs of a permanent myocardial injury from coronary arterial disease like a significant Q wave or depression of the S–T segment are absent from this distinctive cardiogram. When the tracing has recovered, strenuous physical exercise will re-introduce the

deformity as a rule unless the period of immunity from pain has been a long one. Only 10 such tracings were found among the 1370 patients whose symptoms suggested cardiac pain, and it is significant that the eight cardiograms which recovered completely were from this number, while only a small blemish remained in the other two tracings.

Because of the favourable prognosis associated with the mutable electrocardiogram, denoting as it does coronary arteriospasm with temporary cardiac ischæmia rather than lasting coronary occlusion with cardiac infarction, its recognition is a matter of considerable moment to the occasional patient who may exhibit it.

Sir John Parkinson made valuable suggestions on the preparation of this paper.

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SECONDARY R WAVES IN RIGHT CHEST LEADS

BY

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The use of the electrocardiogram as an aid in the diagnosis of right ventricular hypertrophy is a comparatively recent advance. It has been suggested that an electrode placed in a similar position to V4 but to the right of the sternum (V4R) would be of additional value in that it would record right ventricular patterns more accurately than the present chest leads. We have been recording this lead (V4R) routinely for the last year and have frequently had difficulty in assessing the significance of the patterns found, mainly because complexes with secondary R waves often occurred in both normal and abnormal tracings. There is no agreed terminology for describing these patterns but the different terms used and the theories underlying them have been comprehensively reviewed by Katz *et al.* (1950). The complexes have been termed RSR^1 or denoted as showing the presence of an " embryonic r wave " or " incomplete right bundle branch block." A more recent suggestion is that the pattern occurs as the result of " defective intraventricular conduction " which may be " focal " or more widespread (Segers, 1949). The confusion in nomenclature is well illustrated by the term " physiological incomplete right bundle branch block " which aptly reflects the uncertainty as to the significance of this type of pattern.

It was decided to record V4R in a series of normal subjects in order to determine the variations that might be found. In addition, it was felt that a study of records taken from other positions over the right chest might help determine the significance of complexes with secondary R waves.

Material and Methods. Fifty subjects (30 men and 20 women) were studied, their ages ranged from 10 to 75 years. None had symptoms of cardiovascular or pulmonary disease, all had blood pressures within the normal range and their hearts were normal on clinical examination.

All the records were taken on an Elmqvist three-channel recorder.

The leads taken from the right of the chest were initially V5R, V4R, V3R, and V1. V5R, V4R, and V3R were recorded with electrodes placed in similar positions to V5, V4, and V3 but to the right of the sternum. At first these leads were recorded in different phases of respiration, but then it was realized that complexes with secondary R waves were more often found when further leads were taken from the intercostal spaces above and below V5R, V4R, V3R, and V1 with the patient breathing normally. The standard and unipolar limb leads and V3, V5, and V7 were also recorded in each patient.

RESULTS

In V4R, the S wave was always greater than either R deflection; in over half the subjects (52%) the pattern was RSR^1 or RSR^1S^1 and in the remainder was rS. We would stress the necessity of placing the electrode in the correct position, because occasionally we found that small changes in electrode position caused important changes in the configuration of the QRS complex.

The incidence of patterns with secondary R waves in the additional leads was also high (Table I) and in 42 of our 50 subjects (84%) RSR^1 or RSR^1S^1 complexes were found in one or more of the leads taken from the right chest. The distribution is shown as a percentage of the total number of recordings in each position as we recorded fewer leads at the beginning of the series. It will be seen that complexes with secondary R waves are most commonly obtained from the intercostal spaces below V5R, V4R and V3R.

TABLE I

THE INCIDENCE OF PATTERNS WITH SECONDARY R WAVES IN THE DIFFERENT ELECTRODE POSITIONS

Intercostal space above 36%	38%	28%	35%	—
V5R 45%	V4R 52%	V3R 34%	V1 26%	V2 13%
Intercostal space below 55%	61%	61%	35%	—

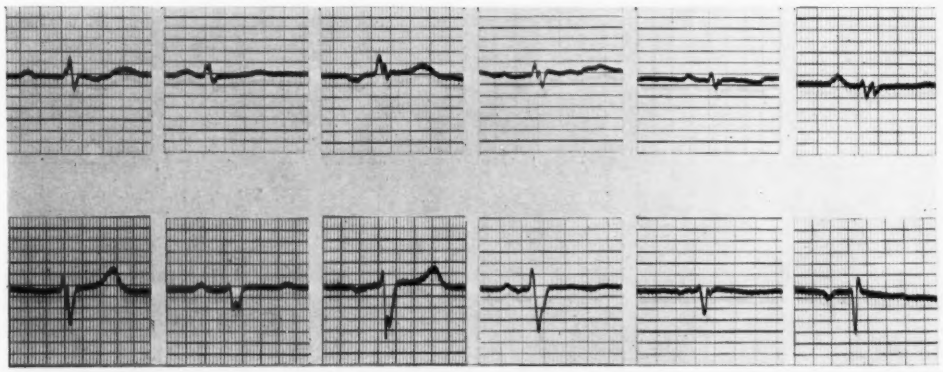

FIG. 1.—Different types of RSR^s and RSR^1S^1 patterns in normal subjects.

Fig. 1 illustrates the different types of RSR^1 or RSR^1S^1 patterns recorded, and in particular shows the wide variation in the position and size of the R^1 wave which was encountered. That these R^1 waves have a common origin was evident from a study of leads recorded simultaneously (Fig. 2) and the variation in pattern is seen to depend almost entirely on the position of the electrode. The " embryonic r wave " in V4R (Fig. 2) is clearly identical with the large secondary R wave recorded from the space below V4R—a complex that might be described as " incomplete right bundle branch block."

All transitions were found between subjects who showed RSR^1 patterns in only one or two leads (Fig. 3) and those in whom it was present in nearly all the right chest leads (Fig. 2).

The duration of QRS in these 42 subjects varied between 0·05 and 0·09 sec. In 22 the duration was 0·08 sec., in 11 it was 0·07 sec., in 5 it was 0·09 sec., in 3 it was 0·06 sec., and in one it was 0·05 sec.

The time of the intrinsicoid deflection in complexes with RSR^1 patterns varied between 0·02 and 0·07 sec. In 14 it was 0·05 sec., in 13 it was 0·06 sec.; in 7 it was 0·04 sec., in 5 it was 0·07 sec., in 2 it was 0·02 sec., and in one it was 0·03 sec.

Large S waves in standard lead I have been considered a feature of tracings showing incomplete or complete right bundle branch block. Prominent S waves were found in standard lead I in 3 of our subjects; in these 3, RSR^1 complexes were found widely in the right chest leads. In 4 others, however, who showed a similar distribution of RSR^1 complexes across the right chest the S waves in lead I were not remarkable.

Of the limb leads, however, the configuration of VR should be more helpful in reflecting patterns

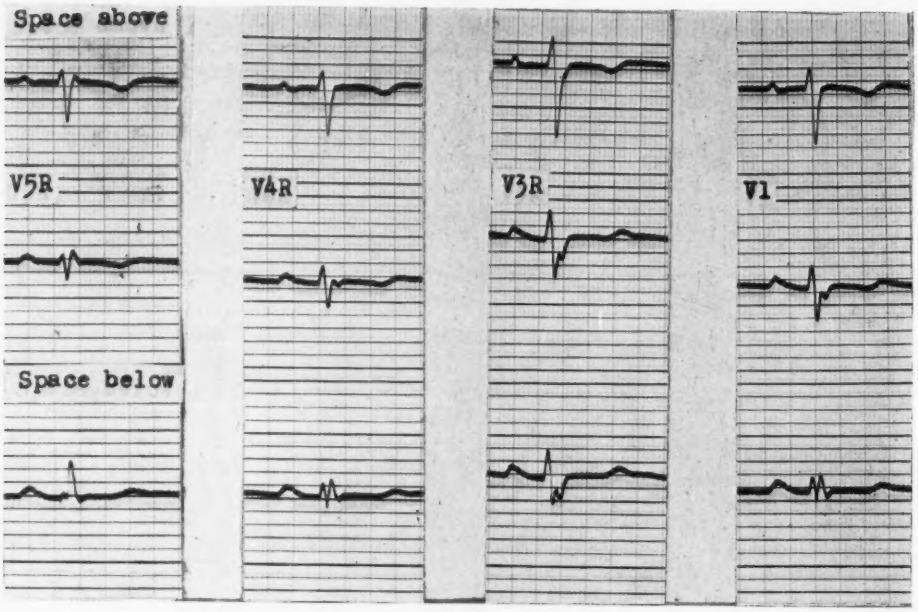

FIG. 2.—Simultaneous records showing common origin of R^1 waves.

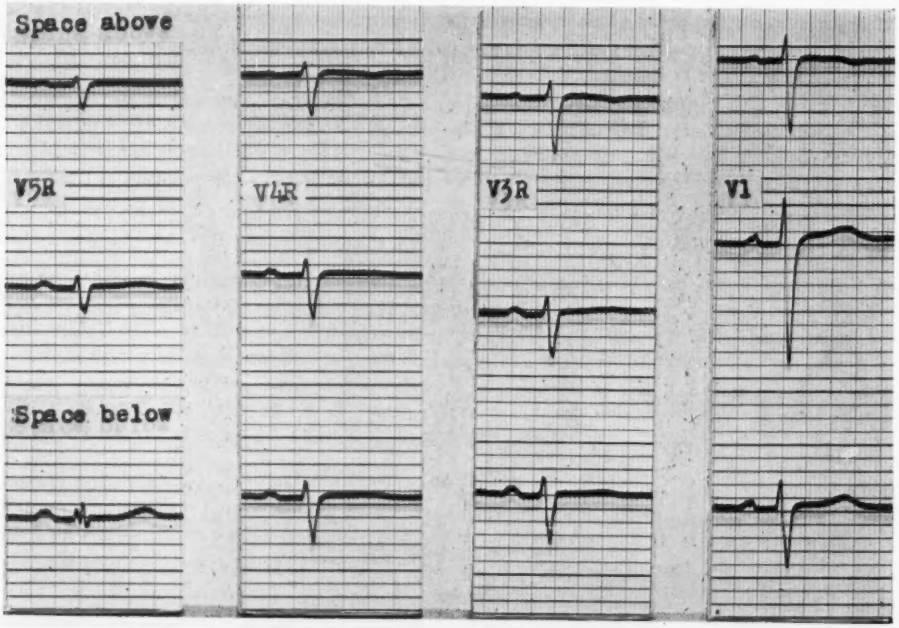

FIG. 3.—RSR^1 patterns in a small number of leads only.

from the right chest. Of the 42 subjects whose chest leads showed complexes with secondary R waves, an rSr^1 pattern in VR was found in 17 and in a further 17 a Qr pattern was present.

Discussion

Irrespective of whether the QRS pattern in V4R was rS, RSR^1, or RSR^1S^1, we always found the S wave to be larger than either R deflection. This finding is useful clinically but we would stress again the importance of positioning the electrode correctly. For example, in Fig. 2 there is a considerable difference between the V4R complex and that recorded from the intercostal space below V4R.

A secondary R wave was present in V4R in over half our subjects and this agrees with the observations of Mounsey *et al.* (1952). The presence of RSR^1 complexes in this or other right chest leads in the majority of normal subjects has not been reported previously. The importance of this finding is firstly that RSR^1 patterns have also been reported in subjects who showed post-mortem evidence of right ventricular hypertrophy (Thomas, 1948; Myers *et al.*, 1948): so that when using the electrocardiogram to make this diagnosis in life, it is important to realize the full range of normal. Secondly, the stigma implied when the term " block " is used to describe complexes of this type makes a review of the terminology pertinent.

Studies made when the electrocardiogram was first introduced were in subjects with abnormal hearts or in animals where conduction was blocked by experimental means; recent work too, has largely concerned patients with clinical heart disease. On this basis, many notched complexes have been explained as being the result of a block or partial delay in conduction. Indeed, if we accept the definition of Barker and Valencia (1949) most of our subjects have incomplete right bundle branch block, a term bearing the implication of some pathological defect in conduction, The same criticism may be made of more recent nomenclature. Segers (1949) has suggested that the cause of patterns of this type is a " block " which is peripheral or " parietal " in that it affects the junction between Purkinje fibres and myocardium or the myocardium itself rather than the conducting system proper. When the complexes are localized (as in Fig. 3) the " block " is said to be " focal " and the defect limited to only a portion of the ventricular wall.

Other workers, however (Wilson *et al.*, 1947), have been doubtful whether there could be any conduction defect in the right bundle branch with a QRS duration of 0·08 sec. or less and a small R^1 wave. Our finding of RSR^1 patterns in most of our subjects confirms this suspicion. It is generally agreed that the initial R wave in V4R and VI is due to activation of the septum from left to right with the S wave resulting from activation of the left ventricle. The R^1 wave must be due to some later stage, activation of some other part of the normal myocardium; that is, there must be some physiological explanation not involving the concept of block and its pathological implications.

It is tempting to believe that the R^1 wave results from normal late activation of at least some part of the right ventricle. Certainly in patients with progressive pulmonary heart disease, an increase in the size of this R^1 wave from normal to abnormal heights has been recorded by Mounsey *et al.* (1952). As long ago as 1915, Lewis and Rothschild noted in dogs that the conus of the right ventricle and the postero-basal portion of the left ventricle are the last parts of the myocardium to be activated. These findings were confirmed by Wilson *et al.* (1930) in their observations on the exposed human heart.

Sokolow and Friedlander (1949) in their work on normal unipolar leads mention the possibility that the second R wave represented activition of the conus of the right ventricle. The only right chest lead they recorded, however, was V1, they found R^1 deflections in only 5 per cent of their subjects and so were uncertain of its real significance.

A study of cavity potentials should be helpful; these have now been recorded from the right atrium and ventricle of normal subjects and terminal R^1 waves have been found. Battro and Bidoggia (1947) concluded that they represented activation of the basal region of the left ventricle and the conus of the pulmonary artery. Sodi-Pallares *et al.* (1947) related them to the late activity of some parts of the right ventricular muscle. Another suggestion—made by Kossmann *et al.* (1950)

—was that the *crista supraventricularis* of the right ventricle may be the source of these secondary R waves.

Our leads showing RSR^1 complexes were recorded from the electrical field of the right ventricle and we feel that our results support the view that activation of the conus is responsible for secondary R waves.

It is not easy to see, however, why RSR^1 patterns are found widely in one subject and only locally in another. Kert and Hoobler (1949) have shown that there is a difference between the times of activation of the two ventricles in normal subjects and that this difference is greater in some subjects than in others. As the QRS complex recorded in any position represents the algebraic sum of the activation potentials of the two ventricles, this asynchronism may give prominence to the potential from the conus, or alternatively this potential may be damped out.

We would suggest, therefore, that QRS complexes of less than 0·10 sec. duration be termed simply RSR^1 or RSR^1S^1 when these patterns are found; they are a normal finding and these are logical descriptive terms.

Summary

In 42 of 50 normal subjects, complexes with secondary R waves (RSR^1) were found in one or more of the many right chest leads recorded.

Many variations of this pattern appeared in different leads taken from the same patient.

The secondary R wave (R^1), may be due to activation of the conus of the right ventricle.

In V4R the S wave was always found to be larger than either R deflection.

We wish to thank Dr. J. F. Goodwin and Dr. M. Zoob for helpful criticism and advice.

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RADIOLOGY OF THE LUNG IN SEVERE MITRAL STENOSIS

BY

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The radiological changes in the lung in heart disease have attracted the attention of cardiologists for many years. Notable contributions have been made by Laubry *et al.* (1929), Roesler (1943), Donzelot and Heim de Balsac (1947), Parkinson (1949), and Zdansky (1953). In mitral stenosis especially, the radiological appearance of the pulmonary vasculature has invited keen attention, but not till the advent of surgery in the treatment of this condition has it been possible to correlate the radiological findings with the severity of the mitral stenosis.

Material and Method

Thirty-three cases of mitral stenosis have been selected in whom the mitral orifice was known to measure one cm. or less in length; so that in each the stenosis was severe. The assessment was made at operation in 30 cases and twice it was later verified at necropsy; in the remaining 3 the valve was examined only at necropsy. Aortic incompetence was diagnosed in 5 cases and mitral incompetence was detected by the surgeon in 13, but never did the electrocardiogram or cardioscopy suggest left ventricular enlargement, so that associated valvular lesions were regarded as slight. Electrocardiographic evidence of right ventricular enlargement was definite in 21, equivocal in 5, and absent in 7 cases. Twelve patients had suffered from right-sided heart failure at some period before operation. Fifteen gave a history of recurrent bronchitis, and two of these had severe emphysema.

Each patient before operation had radiographs that satisfied the criteria of the Medical Research Council X-ray Subcommittee. In 28 of the 33 cases the radiographic examination was made within four weeks of operation or of necropsy.

The films were exposed by a standard technique. The postero-anterior film was taken at a distance of six feet, respiration being halted at the end of a normal, or in some cases a deep, inspiration. The factors employed in the majority of cases were: 300 mA, approximately 65 kV, andone-tenth sec. exposure. Lateral films were taken in all cases, but they contributed little information of value.

Findings

The lung architecture was considered to be abnormal in each case, and the changes that were observed may be described in relation to their anatomical situation under three headings—the hilum, the parenchyma, and the pleura.

The Hilum. In the normal lung, the right and left pulmonary arteries and their subdivisions stand out clearly against the background of a translucent lung (Fig. 1). The margins of the vessels are distinct and on the right side the lumen of the right main bronchus can be seen lying medial to the main descending branch of the pulmonary artery.

In severe mitral stenosis (Fig. 2) the left hilum is frequently concealed by enlargement of the main pulmonary artery and its left branch. The right hilum, on the other hand, is generally visible. It stands out further from the mid line than usual, and is enlarged and clouded. The margins of the main pulmonary artery and its primary branches are ill defined and the bronchial lumen is obscured. Sometimes the hilum merges imperceptibly into the surrounding lung. Great hilar clouding (" hilar congestion ") was observed in 14 of the 33, more moderate clouding in 16, and

FIG. 1.—Slight mitral stenosis, showing normal right hilum. The mitral valve was 3 cm. long and slightly incompetent.

FIG. 2.—Severe mitral stenosis, showing great hilar clouding. The mitral valve was a little less than 1 cm. long.

none in 3 cases. In 23 of the 30 cases with hilar clouding there was also loss of translucency in the surrounding lung. Of the 7 cases where loss of translucency was slight or absent, two had severe emphysema.

The Parenchyma. In health, the lung markings are almost entirely vascular (Fig. 3). The branches of the pulmonary artery can usually be traced to within 1 cm. of the pleura. Often the right inferior pulmonary vein and its tributaries can also be followed and less commonly other parts of the venous system. The periphery of the lung is difficult to analyse with the exception of the costophrenic angles where it is frequently possible to trace vascular aborization to within a few millimetres of the pleura.

In severe mitral stenosis the normal translucency is usually lost (Fig. 4). The margins of the heart and the ribs lose their sharp definition and the outline of the pulmonary arterial branches is obscured. This clouding, greatest in the lower half of the lung, was present in 24 cases. Close scrutiny of the lung structure shows the clouding to be due most commonly to an abnormal profusion of vessels 0·5 to 2 mm. in width. These conceal the larger arteries as fine twigs obscure the branches of a tree. This abnormal vascular pattern was seen, not only in the 24 cases in which loss of translucency was evident from a distance, but also in five cases where the translucency appeared normal or increased; two of these had severe emphysema.

Loss of translucency was frequently associated with the presence of numerous short linear shadows (Fig. 5 and 7). Attention was first drawn to these lesions by Kerley (1951) who noted their presence in silicosis, carcinomatosis lymphangeosa, and hypertension as well as in mitral stenosis. They are distinguished from other shadows of linear appearance by their size, number, distribution, and direction. These lines are 0·3 to 1·0 mm. broad and 5 to 15 mm. long. Their margins are sharp and well defined and they are usually of constant width, though they may be a little broader in the middle than at the ends. They are found most commonly in the costophrenic angles, but when numerous, they extend up the lateral surface of both lungs and may be scattered

FIG. 3.—Slight mitral stenosis, showing normal vascular markings. The same patient as Fig. 1.

FIG. 4.—Severe mitral stenosis, showing loss of normal translucency and septal lines in the costophrenic angle. The same patient as Fig. 2.

profusely over the whole of the lower and middle zones. In the lateral radiograph the lines may be seen lying beneath the anterior chest wall within the middle lobe.

These lesions lie immediately beneath the pleura and at right angles to it. Thus on the costal surface of the lung they are horizontal, and on the diaphragmatic surface they are vertical. In the centre of the lung where the pleura is viewed end-on instead of tangentially they may present a hexagonal pattern. Since there is no doubt that these lesions correspond to the interlobular septa (see *Discussion*) they may appropriately be termed septal lines or septal shadows.

Septal lines were found in 25 cases. In none were they the sole abnormality, though in several instances where either hilar clouding or loss of translucency were equivocal they provided conclusive evidence of an abnormal lung pattern. When scanty, these lesions may easily be overlooked unless the costophrenic angles and adjacent areas are diligently scrutinized.

Narrowing of the distal half or two-thirds of the pulmonary arterial tree in cases of mitral stenosis with severe pulmonary hypertension has been demonstrated by angiography (Goodwin *et al.*, 1952). This observation has proved of limited application in the study of the plain radiograph for two reasons. In the first place, the arteries to the lower half of the lung, where the attenuation is most pronounced, are often obscured. Secondly, the size of the arteries shows wide variation in health (Lodge, 1946).

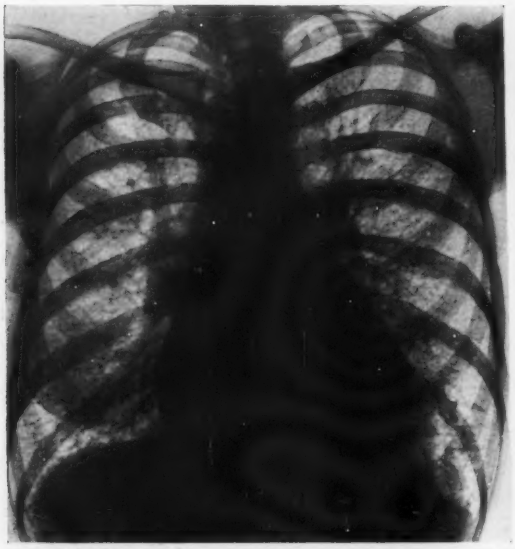

FIG. 5.—Severe mitral stenosis, showing septal lines extending up the lateral surface of both lungs and osseous nodules in the left lower zone. The mitral valve was 1 cm. long (see Fig. 7).

FIG. 6.—Severe mitral stenosis, showing normal translucency and absence of hilar clouding; the intrapulmonary arteries are greatly narrowed. The mitral valve was 1 cm. long (see Fig. 8).

In the present series there were nine patients in whom most of the arteries within the right lung could be seen clearly enough to permit an assessment of calibre. In two of these, all the vessels within the middle and lower lobes were narrowed to a striking degree. Once this feature constituted the sole abnormality of the lung pattern (Fig. 6 and 8). In 4 cases the calibre was regarded as borderline, and in the remaining three the arteries were normal.

The main pulmonary veins were seldom recognized either because they were obscured by loss of translucency within the lung or because they were hidden by the enlarged heart shadow.

Linear streaks radiating out from the hilum into the lower or middle lobe of the right lung, similar to those described by Kerley (1951) in silicosis, were seen twice. Other abnormal features observed in the lung parenchyma included pulmonary infarcts in three cases, a picture suggesting hæmosiderosis in one case, and disseminated osseous nodules in one case.

The Pleura. A large pleural effusion was observed once only. Repeated aspiration was required before operation, but thereafter no further paracentesis was necessary. One other case had a trace of fluid in the costophrenic angle, but it disappeared within a week.

Thickening of the interlobar fissures was noted in 12 cases. Although best appreciated in the lateral view, it was usually evident in the postero-anterior view also; most commonly as an abnormal prominence of the horizontal fissure; less frequently as a thickening of the inconstant pleural fold separating the retrocardiac (inferior accessory) lobe from the remainder of the lower lobe. In the two patients with severe emphysema, there was extensive old pleurisy over both lower lobes.

Severe Mitral Stenosis without Hilar Clouding. There were three patients in whom hilar clouding was absent or equivocal. In one, there was slight loss of translucency and faint septal lines. In another, similar lines were present without loss of translucency, and in the third both were absent. The vascular pattern was abnormal in all three: in one, all the branches of both main pulmonary arteries were considerably narrowed, and in the other two the arteries within the lower halves of both lungs were obscured by a profusion of small vessels.

FIG. 7.—Contact print of part of right lung to show septal lines. The same patient as Fig. 5.

FIG. 8.—Contact print of part of right lung to show narrowed arteries. The same patient as Fig. 6.

Clinically, these patients were indistinguishable from those with pronounced radiological changes. One had severe pulmonary hypertension. Another suffered from recurrent right heart failure although the electrocardiogram showed no evidence of right ventricular hypertrophy. The third had never suffered from congestive failure; the right ventricular pressure at rest was scarcely raised and the cardiogram showed only slight right ventricular hypertrophy. In none was any evidence of tricuspid or pericardial disease found.

Serial Radiography. Two patients were under observation for over three years before surgical treatment and in both the lung architecture was abnormal from the start. During the period of

observation, hilar clouding increased and fresh septal lines appeared. In one there was a sudden temporary deterioration due to acute pulmonary œdema. Two years later, during a period of rest in bed and digitalis medication before operation, the septal lines decreased though the hilar clouding and loss of translucency persisted.

No definite change in lung pattern was detected in patients followed for periods of less than one year. Rest in bed with or without salt depletion produced slight or moderate improvement in the radiograph, irrespective of the presence of right heart failure. In one case a small effusion cleared. In several instances pleural thickening disappeared and septal shadows became less conspicuous though in none was there a reversion to anything approaching a normal pattern. Thus, the pulmonary changes in severe mitral stenosis are persistent but not fixed. Medical treatment may lead to temporary improvement, but the general trend is one of slow deterioration.

Discussion

An abnormal lung pattern was found in each of the 33 cases of severe mitral stenosis, but in three, hilar clouding, loss of translucency and septal lines were either absent or equivocal and the only definite abnormality was in the vascular pattern.

An adequate radiograph is essential if slight changes are to be detected. Loss of definition in the hilum and the arterial tree may be produced by pulsation, so the exposure should be as short as possible. With modern apparatus 0·05 sec. is frequently possible and it should never be necessary to exceed 0·1 sec. No conclusion should be drawn from any radiograph in which the outline of the upper ribs, the diaphragm, and one or other cardiac border is not sharp.

The salient features of the lung radiograph in mitral stenosis have long been recognized, but Kerley's description of the linear shadows has provided an additional sign, the importance of which may be measured by the fact that it was noted in no less than three-quarters of the cases. Once the characteristic appearance of the septal line has become familiar—its thread-like form, horizontal direction, and predeliction for the costophrenic angles—it is easily recognized. Scanty lesions in obese patients may be missed if the film is not taken in full inspiration or is under-exposed. Where the costophrenic angles are concealed by the breasts, it may be helpful to take a film with the breasts raised, or alternatively to use a grid or take an antero-posterior radiograph.

Small vessels are sometimes well seen running laterally in the costophrenic angles, and it is important not to mistake these for septal lines. Differentiation is usually possible if attention is paid to the following points (Fig. 9).

(1) The margins of vessels are blurred while septal lines are sharp and well defined.

(2) Small vessels can be seen joining a larger vessel proximally. Septal lines seldom join a larger vessel and if they do so, the difference in character between the well-defined line and the " softer " vessel is evident.

(3) Vessels taper toward the periphery whereas the linear shadows are of constant width or else widen slightly in the middle.

(4) Vessels are part of a ramifying system, junctions being indicated by dots formed by branches viewed end-on. Septal lines do not branch and therefore dots are absent.

Septal lines correspond both in size and distribution with the interlobular septa, a fact that may readily be appreciated by an examination of lung slices prepared by the technique of Gough and Wentworth (1949). These septa consist of ingrowths from the subserous areolar tissue that invests the lung. They are traversed by tributaries of the pulmonary venous system and also by the lymphatic channels that link the deep lymphatic system with the subpleural network. The prominence of the interlobular septa in mitral stenosis must therefore be due to enlargement of one or more of these structures. The fact that in some cases septal shadows persist unchanged after relief of the stenosis is difficult to reconcile with the view that they are due to lymphatic or venous engorgement. An acceptable explanation must take into account both the fluctuation in size that is observed in some cases and the persistence following surgical treatment in others. We

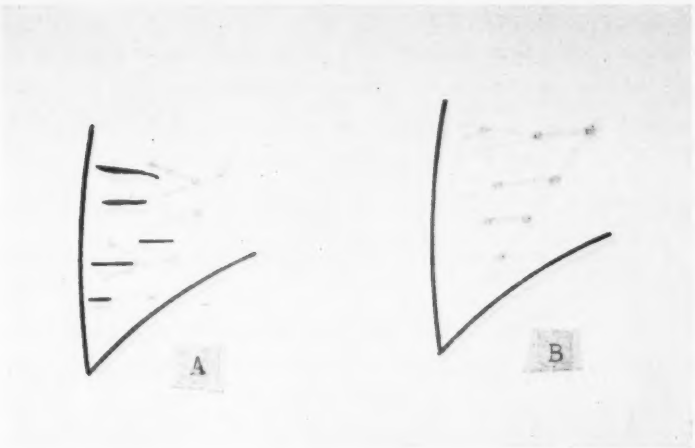

FIG. 9.—Septal lines contrasted with blood vessels in the costophrenic angle (diagrammatic). (A) Septal lines. (B) Blood vessels.

think that the enlargement of the septa is due to swelling of the areolar tissue, at first from œdema and later from fibrosis.

It is perhaps necessary to emphasize that although the radiological pattern as a whole may prove to be peculiar to mitral stenosis, no single feature is diagnostic of it. A similar appearance of the hilum is seen in left ventricular failure and in emphysema and bronchitis. Prominent septal lines are found most frequently in mitral stenosis, but they are also seen in some types of pneumoconiosis and in carcinomatosis lymphangeosa. Slender lines are not uncommon in hypertensive heart failure. Loss of translucency is seen in heart failure from a variety of causes, and attenuation of the peripheral pulmonary arteries has been noted in primary pulmonary hypertension. It is not claimed that the presence of these radiographic abnormalities indicates mitral stenosis, but rather that their absence is strong evidence against severe mitral stenosis.

There are many gaps in our understanding of the pulmonary changes in mitral stenosis. Perhaps the most obvious is our inability to account for the wide variation in intensity of these changes in patients with an identical degree of mitral stenosis. Another aspect on which our information is inadequate concerns the effect of these changes on respiratory function. Again, what is the morbid anatomy underlying hilar clouding, arterial narrowing, and the profusion of small vessels? Which lesions are reversible and which are irreversible? The answers to these questions may have an important bearing on the selection of patients with mitral stenosis for surgical treatment.

SUMMARY AND CONCLUSION

The radiographic appearances of the lungs were studied in 33 patients with rheumatic mitral stenosis in whom, at operation (or necropsy), the maximum diameter of the mitral valve was 1 cm. or less. Twelve had suffered from right heart failure.

The lung architecture was abnormal in each patient, though the degree of abnormality varied widely, being slight in some and considerable in others. Hilar clouding was present in 30 and loss of translucency in 24. Pleural involvement was evident in 15, two of whom had a right-sided effusion. The vascular pattern was abnormal in 30 patients. Most commonly the intrapulmonary arteries were obscured by a profusion of small vessels, but occasionally these arteries were well-defined and severely attenuated. Septal lines were found in 25 cases and though never the sole

abnormality they were sometimes the most impressive. Serial radiography showed the changes to be persistent and slowly progressive.

A normal lung architecture is inconsistent with a diagnosis of severe mitral stenosis.

The patients were under the care of Dr. William Evans or Dr. Wallace Brigden, to both of whom, as well as to Dr. Peter Kerley, I am indebted for helpful criticism. Mitral valvotomy was performed either by Mr. Vernon Thompson or Mr. Geoffrey Flavell.

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A NEW METHOD OF DETERMINING THE DEGREE OR ABSENCE OF MITRAL OBSTRUCTION :

AN ANALYSIS OF THE DIASTOLIC PART OF INDIRECT LEFT ATRIAL PRESSURE TRACINGS

BY

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For some years we have been interested in the *y* descent of the venous pulse. Until quite recently conspicuous diastolic collapse of distended cervical veins was believed to be pathognomonic of chronic constrictive pericarditis. The sign was first described by Friedreich (1864) and attributed by him to the sudden negative intrathoracic pressure created by outward rebound of the chest wall when released from the inward pull of ventricular systole in cases of adherent pericardium. A jugular phlebogram showing the phenomenon was published by Mackenzie in 1902; he called the diastolic trough Z, and accepted Friedreich's explanation. Years later, cardiac catheterization revealed that a marked early diastolic pressure dip in the right ventricle accompanied the steep *y* descent of the venous pulse (Bloomfield *et al.*, 1946); it was at first attributed to the same cause (Eliasch *et al.*, 1950). Hansen *et al.* (1951), however, proved that the dip was independent of the movements of the chest wall, and suggested that it was due to an unusually high pressure gradient between atrium and ventricle at the end of the isometric relaxation phase; early diastolic filling was therefore very rapid and the maximum capacity of the ventricle was reached quickly.

It was soon apparent, however, that Friedreich's diastolic collapse was not confined to Pick's disease, but occurred in severe right ventricular failure from any cause: we have recorded it in hypertensive heart failure, ischæmic heart failure, isolated myocarditis, and heart failure from severe pulmonary hypertension (Wood, 1954); in some of these cases there was convincing evidence of tricuspid incompetence, but by no means in all. The steep *y* descent following *v* was associated with a dip and plateau in the right ventricular diastolic tracing. Indirect left atrial pressure tracings, using the wedged catheter technique, showed the same steep *y* descent in cases of left heart failure with high pulmonary venous pressures.

The next step was the discovery that a steep *y* descent did not occur in tricuspid stenosis despite a high filling pressure; instead of Friedreich's abrupt trough, the venous pressure fell relatively slowly after the summit of *v*, and failed to rise again before the next atrial or ventricular contraction. Similarly, a relatively slow and steady rise of pressure replaced the dip and plateau pattern in the right ventricular tracing (Wood and Gibson, 1954). It followed that Friedreich's sign was no more than evidence of a potentially high right atrio-ventricular pressure gradient at the end of the isometric relaxation phase, a state of affairs highly characteristic of Pick's disease but also occurring, though usually in less florid form, in any condition with an unusually high venous filling pressure, *provided there was no obstruction at the atrio-ventricular (tricuspid) orifice.*

At about this time, towards the end of 1953, we were searching for a better method of deciding whether mitral stenosis or incompetence was dominant when there was clinical evidence of both. Up till then the interpretation of indirect left atrial pressure tracings had not served to distinguish them; but attention had always been directed to the systolic part of the curve. In the light of the

observations described above, we wondered whether the diastolic part of the tracing would not be more informative. In fact, this proved to be so, and it is the purpose of this paper to present data indicating that the behaviour of the *y* descent in indirect left atrial pressure tracings provides good evidence of the presence or absence of obstruction at the mitral orifice.

Terminology. " Indirect left atrial " is used synonymously with " wedged pulmonary arterial " and " pulmonary capillary venous " in referring to pressure, acceptance of their unity in both phase and magnitude being thereby implied (Hellems *et al.*, 1949; Dow and Gorlin, 1950; Epps and Adler, 1953). " *a* " and " *v* " are the two main positive deflections of the left atrial pulse associated respectively with atrial contraction and with passive atrial filling against a closed mitral valve; the subsequent decline of atrial relaxation and atrio-ventricular diastolic flow are termed " *x* " and " *y* " (Mackenzie, 1902).

Methods

Indirect left atrial tracings were obtained by wedging a cardiac catheter during inspiration in a distal branch of the pulmonary artery and recording the pressures by means of a Sanborn electromanometer employing hydraulic damping (Hansen, 1949) and a Polyviso direct-writing recorder. In some instances, inclusion of a filter device in the electronic circuit permitted variable high-frequency attenuation. Manometer sensitivity was adjusted so that a deflection of 40 mm. above the base-line represented a pressure of 40 mm. Hg in the system; but when the pressure was very high the sensitivity had to be reduced so that a deflection of 40 mm. represented a pressure of 100 mm. Hg. Calibration was recorded at the end of each section of tracing together with the zero level (sternal angle) and an electronically determined mean pressure. The speed of the paper, on which an electrocardiogram was simultaneously recorded, was 25 mm. per second.

Pulmonary and peripheral arterial blood samples were analysed for oxygen unsaturation in a Haldane blood-gas analysis apparatus; cardiac output calculations were based on the arterio-venous oxygen difference so determined and a Benedict-Roth estimation of the oxygen uptake at the time of catheterization.

It was usually possible to record acceptable tracings in the wedged position, although several attempts might be required to do so and careful inspection of the pulse contour at the time of recording was indispensable. Factors that sometimes militated against success were considerable enlargement of the right heart (so that the catheter was too short); too soft or too large a catheter (greater than size U.S. No. 7); and extreme pulmonary hypertension (causing loss of normal tapering of the pulmonary arterial tree).

For analysis, the tracings were required to be venous in pattern and of undistorted wave form (Wood, 1952). High-frequency sound deflections were superimposed on all but grossly overdamped records; although these did not as a rule obscure the venous pulse, some distorted tracings had to be discarded on this account. Doubt did not often exist as to whether the manometer was reflecting left atrial or pulmonary arterial pressures, but an appreciable increase in the slope of the *y* descent accompanying the expiratory rise in left atrial pressure confirmed its venous origin. In general, the clearest and most accurately measurable pulse waves were recorded during held expiration, with the atrial pressure at its maximum.

For purposes of measurement, vertical intervals were interpolated with the eye to 0·5 mm. and time intervals to 0·25 mm. (0·01 sec.). The average rate of the *y* descent (R*y*, in mm. Hg per sec.) was calculated as

$$\frac{(p_1-p_2)\text{ mm.}\times\text{calibration factor}}{(t_2-t_1)\text{ sec.}}$$

where p_1 is the first point on the *v* wave free from sound artefact at which a pressure fall is perceptible and p_2 is either the point at which the descent first reaches its subsequent isotonic level, or, if it continues throughout diastole until interrupted by atrial contraction or mitral valve closure, the last point on the slope to be unobscured by these events; and t_1 and t_2 are the corresponding points on the time scale. In the former case, the brief terminal dip below the isotonic sometimes displayed by the *y* descent was ignored in calculating R*y*, p_2 being taken immediately before its occurrence (Fig. 1). These points were adopted arbitrarily for purposes of standardization. As indicated below, it became desirable to relate the rate of the *y* descent to the absolute pressure represented by the *v* wave. The ratio between the two (R*y*/*v*) was then derived by inserting the height of *v* in millimetres above the zero reference point (i.e. p_1) into the denominator and removing the calibration factor from the numerator:

$$\text{R}y/v=\frac{(p_1-p_2)\text{ mm.}}{p_1\text{ mm.}\times(t_2-t_1)\text{ sec.}}$$

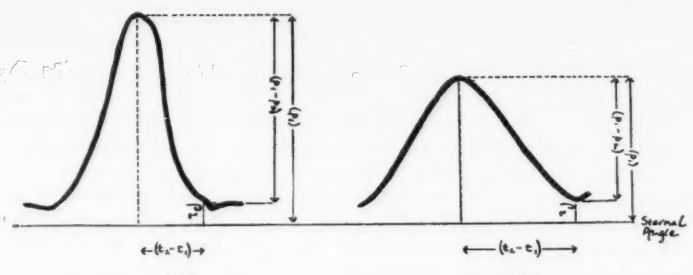

FIG. 1.—Diagram of typical *v* waves in indirect left atrial pressure tracings in mitral incompetence (A), and mitral stenosis (B), illustrating how the rate of *y* descent is measured (see text).

Material. The study is based on an analysis of 54 wedged pulmonary arterial pressure records obtained during right heart catheterization. All patients were suffering from mitral valve disease and were undergoing this investigation in order that the appropriateness of surgical treatment might be assessed. They form part of a series of such cases, the clinical and other features of which have already been reported in detail (Wood, 1954). According to the nature of the mitral lesion, they fall into five groups, as follows.

(1) Pure mitral stenosis severe enough to warrant valvotomy, where that diagnosis was confirmed, and the absence of incompetence established at cardiotomy (23 cases).

(2) Mitral stenosis of comparable severity in which a trivial degree of incompetence was detected at operation (5 cases).

(3) Mitral stenosis combined with moderate incompetence, so classified on the operative findings in 2 and on clinical grounds in 6 cases (8 cases).

(4) Mitral stenosis with considerable incompetence, the latter being considered the dominant lesion. In 2 this assessment was surgical, in 8 clinical (10 cases).

(5) Pure or almost pure mitral incompetence, the diagnosis being clinical in 4 and surgically confirmed in 4 (8 cases).

The criteria for the clinical diagnosis of mitral incompetence have been discussed elsewhere (Wood, 1954).

THE LEFT ATRIAL PULSE IN MITRAL VALVE DISEASE

Preliminary Observations. That the amplitude of *v* by itself does not usefully distinguish between dominant mitral stenosis and dominant incompetence was confirmed by the results of a pilot study in which tracings from known examples of the two conditions were compared (Table I). The samples used were small (6 cases of incompetence, 8 of stenosis) and influenced by selection in several ways, but it was considered unlikely that a characteristic of practical value would fail to show a clear-cut difference between the groups. In fact, as Table I indicates, although the expected differences occurred—the rate of pressure rise and the amplitude and height of *v* all being

TABLE I

MEASUREMENTS OF THE "V" ASCENT AND "Y" DESCENT IN MITRAL STENOSIS AND INCOMPETENCE

Mean values	"V" Ascent			"V"	"Y" Descent		
	Rise mm. Hg	Time sec.	Rate mm./sec.	Peak mm. Hg	Fall mm. Hg	Time sec.	Rate mm./sec.
Stenosis ..	10·4	0·38	31·5	23·6	10·8	0·41	27·6
Incompetence ..	17·0	0·32	59·7	26·5	16·5	0·25	68·3
Difference ..	+ 6·6	−0·06	+28·3	+ 2·9	+ 5·7	−0·16	+40·7
t = ..	1·47	0·83	1·59	0·45	1·42	3·98	2·61
p	>0·1	>0·1	>0·1	>0·1	>0·01	>0·01	>0·05

greater among the incompetence cases—these were small and showed considerable variability among individuals; and on application of the "*t*" test only the differences in time of inscription of the *y* descent and its calculated rate of fall proved significant at the 95 per cent level of probability.

Fig. 2 and 3 are idealized curves drawn through the mean values of these observations and represent the average form of the *v* wave and *y* descent in stenosis and incompetence respectively. The pattern is similar in sinus rhythm and atrial fibrillation. In incompetence the *y* descent is rapid and the rate of fall tends to decrease in its lower part as it approaches a flat isotonic level; unless diastole is much abbreviated, such a level constantly precedes the next cycle. In contrast, the curve in stenosis is flatter, and although the average height of the *v* wave above the sternal angle is little less, the diastolic fall-off in pressure proceeds more gradually; a decrease in the rate of fall is not usually apparent in the lower part of the *y* descent and there is no isotonic interval before the onset of the next *a* wave or first sound artefact.

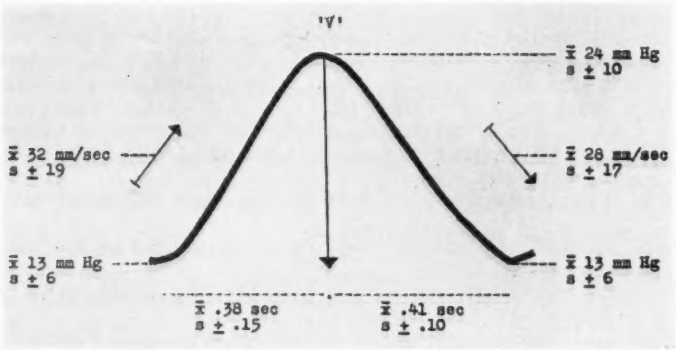

FIG. 2.—Drawing of typical *v* wave in mitral stenosis based on the mean of eight observations. The R*y*/*v* ratio is 28/24 or 1·17. $\bar{x}$ is the mean of eight observations and *s* the standard deviation.

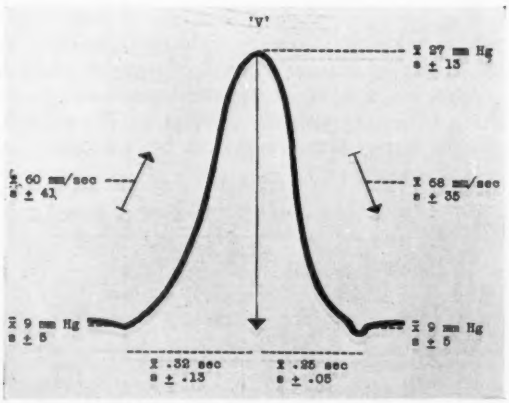

FIG. 3.—Drawing of a typical *v* wave in mitral incompetence based on the mean of six observations. The R*y*/*v* ratio is 68/27 or 2·5. $\bar{x}$ is the mean of six observations and *s* the standard deviation.

The atrial pressure pulse thus appears to reflect the pattern of ventricular filling. In the presence of obstruction to forward flow at the mitral orifice, the left ventricle fills slowly and inadequately despite development of a large pressure head, and flow tends to continue throughout diastole (Wiggers, 1923). When records showing atrial fibrillation are examined, the *y* descent is seen to continue even during the longest diastolic intervals (Fig. 4, upper), confirming that a diastolic pressure gradient across the mitral valve never ceases to exist. In mitral incompetence, the combination of a high atrial pressure at the end of systole with no forward obstruction produces rapid and early filling of the left ventricle and a correspondingly rapid *y* descent; the form of the latter and the presence of the subsequent isotonic plateau suggests that atrio-ventricular pressure equalization is achieved shortly after the opening of the valve and that atrial pressure thereafter follows that in the relaxing ventricle. Typical examples of the two patterns in indirect left atrial tracings are illustrated (Fig. 4 and 5).

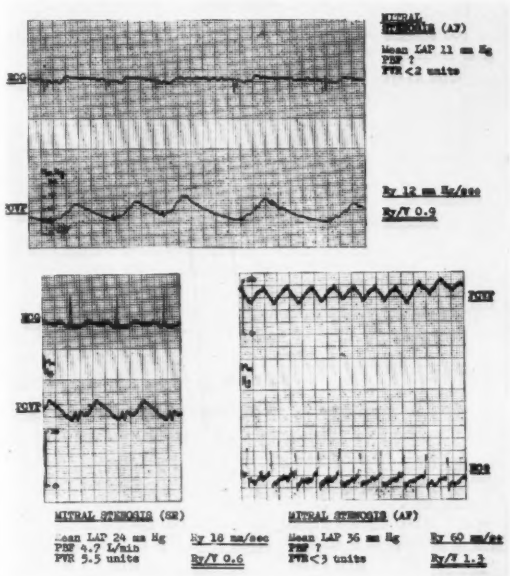

FIG. 4.—Indirect left atrial pressure tracings in three cases of mitral stenosis showing low R*y*/*v* ratios.

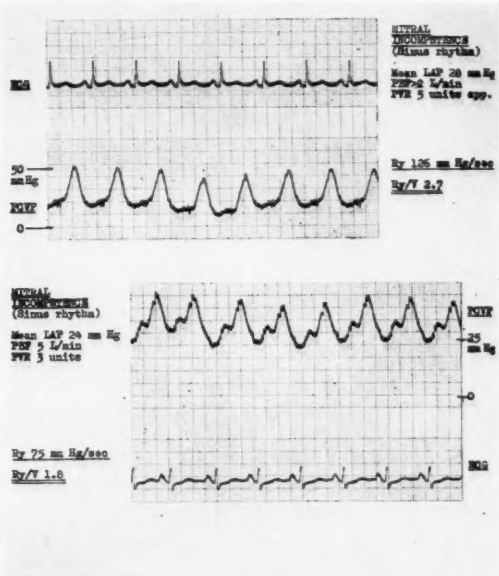

FIG. 5.—Indirect left atrial pressure tracings in two cases of mitral incompetence with normal rhythm showing high R*y*/*v* ratios.

From these preliminary observations, it seemed possible that an expression of the behaviour of the *y* descent might assist in the evaluation of wedged pulmonary arterial records. Although the time occupied by the inscription of the *y* descent had yielded a highly significant difference between the stenosis and incompetence groups (Table I), the tracings analysed had been selected to some extent for clarity of diastolic interval; and when applied to unselected examples of mitral stenosis, this measurement itself was dependent on the length of the diastolic intervals available for study. The calculated average slope of the *y* descent (R*y*) was not so dependent, but was a more variable quantity and separated the groups less sharply. Moreover, it failed to remain constant even in the same record, tending to vary with the height of the preceding *v* wave during the pressure fluctuations associated with respiration (Fig. 6) or induced by exercise. As might be expected, it proved necessary to relate R*y* to the left atrial diastolic pressure head in order to obtain

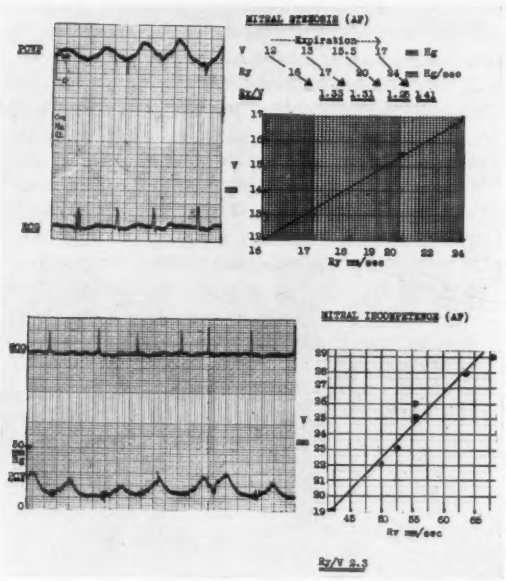

FIG. 6.—Graphs showing the effect of the height of the *v* wave on the rate of *y* descent. It will be seen that the rate of *y* descent is directly proportional to the height of *v* in any given tracings.

a stable expression. The simple ratio R*y*/*v* was derived since this appeared to depart little from linearity in individual records. A series of 57 repeated observations made on tracings from 19 cases confirmed the reproducibility of R*y*/*v*, which was more than twice that of R*y* by itself (respective coefficients of variation approximately 9% and 19%). As the value also yielded a highly significant difference between the initial test groups, the possibility that it might prove a useful index of the situation at the mitral valve was further explored.

RESULTS

R*y* and R*y*/*v* were calculated for all cases available for the present study. When R*y* is plotted against *v*, the general correlative trend of the two and the consistently higher value of their ratio in the presence of incompetence are confirmed (Fig. 7). With one exception (Case N. 347, R*y*/*v*=2·4), the ratio was less than 1·5 in examples of pure stenosis, whereas it invariably exceeded this figure in the presence of moderate incompetence ; in all the 8 cases where incompetence was the only significant lesion the ratio was greater than 2·2. If the single outlying observation (which is unexplained) is excluded, the mean R*y*/*v* values are as follows.

Group 1. Pure mitral stenosis (22 cases), 0·81 (SD±0·36).
Group 2. Mitral stenosis with trivial mitral incompetence (5 cases), 1·06 (SD±0·43).
Group 3. Mitral stenosis with moderate mitral incompetence (8 cases), 1·8 (SD±0·73).
Group 4. Mitral stenosis with considerable mitral incompetence (10 cases), 2·3 (SD±0·56).
Group 5. Mitral incompetence with insignificant mitral stenosis (8 cases), 3·1 (SD±1·2).

That is, R*y*/*v* increases with the presence and degree of mitral incompetence (Fig. 8). The difference between the first two groups is small and not statistically significant; the ratio in these 27 cases considered together yields a mean value of 0·85 (±0·38) about which it tends to form a normal

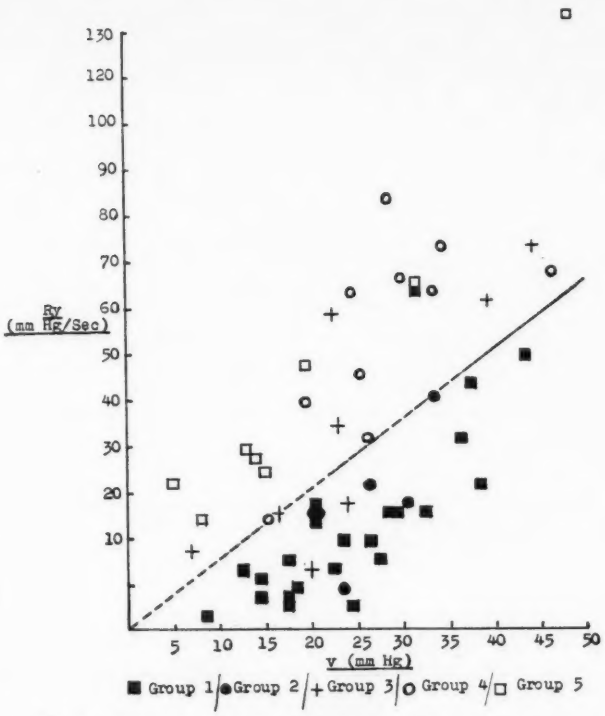

FIG. 7.—Graph showing the relationship of Ry to v in the five groups of mitral valve disease mentioned in the text. The open squares or circles represent cases with pure or dominant mitral incompetence; the black squares or circles represent pure or dominant mitral stenosis; group 3 is borderline. In addition to the general correlative trend between Ry and v, the consistently higher values for the Ry/v ratio in the cases with incompetence is well shown.

distribution (Fig. 9). It may therefore be deduced that Ry/v will be less than 1·6 in 95 per cent of cases * of serious mitral valve disease where incompetence is either absent or insignificant in degree and that a greater value will imply the presence of appreciable regurgitation with equal probability. Although in groups 4 and 5 all values were above this figure in the present series of observations, the data are too few to permit estimation of a useful lower confidence limit beyond which incompetence may be expected to be absent, and are further limited by the fact that the diagnosis was only controlled by surgery in a proportion. The 8 observations in group 3 range between 0·6 and 3·3 but in only two was the classification known with certainty to be correct; since clinical assessment is most difficult in such cases the group was probably more heterogeneous than the others and may include patients who would have been placed in another category after cardiotomy. Further studies are required to elucidate the distribution of Ry/v in this borderline group.

The pulmonary vascular resistance was raised above normal in 23 of the 54 cases, in 5 to the extreme grade (Table II). The results in these did not differ significantly from those in the remainder.

In 30 of the surgical cases the data are sufficient to allow comparison of the Ry/v ratio with the degree of stenosis as estimated at operation on the one hand, and with that predicted from the

* Not greater than 1·7 with 99 per cent probability.

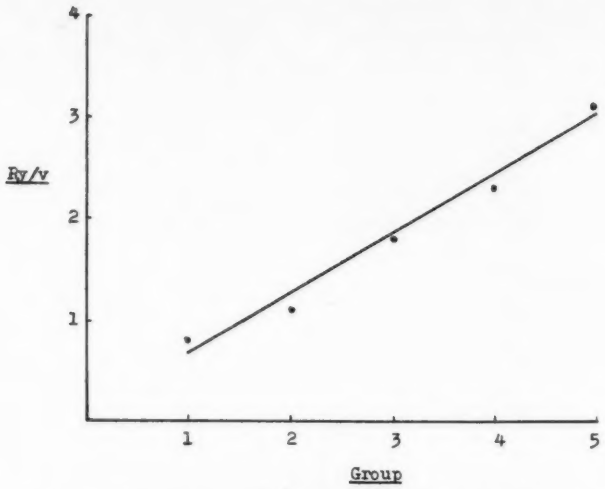

FIG. 8.—Composite graph showing that the Ry/v ratio increases with the presence and degree of mitral incompetence. The five groups are defined in the text.

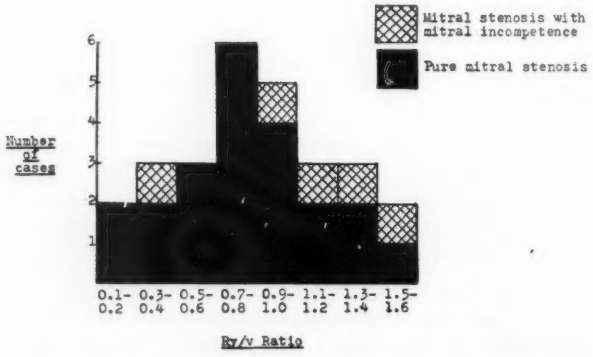

FIG. 9.—Frequency of distribution of the Ry/v ratio in cases of pure mitral stenosis and mitral stenosis with trivial incompetence (groups 1 and 2).

cardiac output and the mean left atrial pressure on the other. On the basis of the surgical assessment, they have been divided into four grades (Wood, 1954) : extreme stenosis (orifice about $0{\cdot}5 \times 0{\cdot}3$ cm.), stenosis tighter than average (about $0{\cdot}75 \times 0{\cdot}4$ cm.), average stenosis (about $1{\cdot}0 \times 0{\cdot}5$ cm.) and less than average stenosis (not less than $1{\cdot}25 \times 0{\cdot}75$ cm.). Although these figures probably underestimate the true dimensions, it may be assumed that they bear a fairly constant relation to them, and to each other. The results of the comparison are shown in Table III. In the first three grades, the expected valve area from the hydrodynamic formula of Gorlin and Gorlin (1951), the simple ratio of cardiac output to mean left atrial pressure (Wood, 1954), and Ry/v show

upward trends, the slope of which is strikingly similar in each (Fig. 10). Significant incompetence was absent in all but three instances. In the fourth grade, however, where examples of dominant incompetence were in the majority, Ry/v rises disproportionately to the other expressions. If the cases in this grade are considered individually (Table IV), both this increase and the greater variability of Ry/v appear to reflect orifice area more truly. While the data are few, they are consistent with the expected disparity between systemic output and valve flow in mitral regurgitation; they support the validity of both methods of assessment in uncomplicated stenosis, and suggest that in combined lesions the Ry/v ratio remains an index of forward area.

TABLE II

DISTRIBUTION OF RAISED PULMONARY VASCULAR RESISTANCE

Group	Pulmonary vascular resistance (PVR units)		
	4·0–5·8	6·0–9·9	10–30
1	4	4	3
2	–	1	1
3	4	1	–
4	2	1	–
5	–	1	1
Totals ..	10	8	5

TABLE III

COMPARISON OF ORIFICE AREA AGAINST Ry/v, CALCULATED MVA AND CO/LAP (MITRAL) INDEX

Surg. estimate (deg. of stenosis)	No.	Group 1 2 3 4 5	Ry/v Mean±SD	MVA cm.² Mean±SD	CO/LAP% Mean±SD
Extreme (0·5×0·3 cm.)	7	5 2 – – –	0·77 0·43	0·84 0·3	16 5·4
Tight (0·75×0·4 cm.)	4	2 1 1 – –	0·85 0·45	0·95 0·17	19 4·4
Average (1·00×0·5 cm.)	13	9 2 1 1 –	1·0 0·49	1·09 0·38	24 8·7
Mild (>1·25×0·75 cm.)	6	2 – – 1 3	2·9 1·96	1·4 0·61	31 13

MVA=Mitral valve area in cm.² calculated from hydrodynamic formula (Gorlin and Gorlin, 1951).
CO/LAP Index=Cardiac output (L/min.)×100/mean LA pressure (mm. Hg).

TABLE IV

LESS THAN AVERAGE STENOSIS: COMPARISON OF ORIFICE AREA AGAINST Ry/v, CALCULATED MVA AND CO/LAP INDEX

Case serial	Group	Surg. estimate * MV area (cm.²)	Ry/v ratio	Calculated MVA (cm.²)	CO/LAP Index
N 453	1	0·95 approx.	0·9	1·7	32
N 553	1	0·95 approx.	0·8	0·7	18
N 826	4	1·50 approx.	2·2	1·9	27
N 509	5	? (>1·0)	2·6	1·6	43
B 74	5	2·25 approx.	6·2	2·0	48
B 191	5	? (>1·0)	2·3	0·6	17
Correlation coefficient with surg. estimate of area in 4 cases where stated			r=0·74	r=0·50	r=0·51

* Arbitrary value obtained by multiplying estimated length and breadth of orifice: relation to true orifice area is unknown.

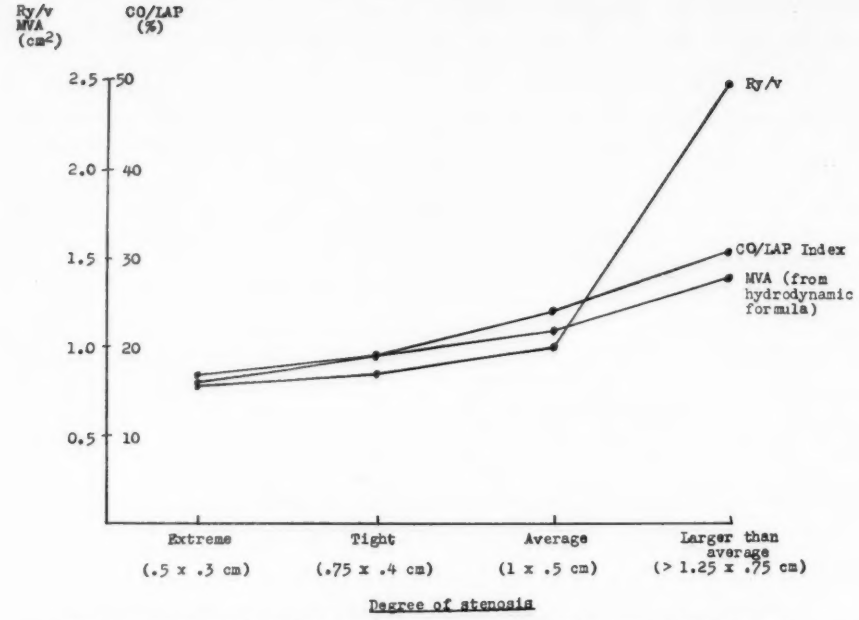

FIG. 10.—Relationship of Ry/v ratios, calculated mitral valve area (Gorlin), mitral index (Wood), and surgically assessed degree of stenosis.

Separate determinations indicate that the mean of the Ry/v values from four wave complexes may be trusted within the limits of about $\pm 0{\cdot}17$. Falsification of the y slope by respiratory pressure swing is occasionally revealed in anomalous observations; these were excluded in making this estimate, which otherwise takes account of all sources of error. The ratio is independent of the sensitivity at which the tracing is recorded, and therefore of inaccuracies in calibration; but precise determination of the zero reference level is essential, since manometer zero drift may involve appreciable error. In this connection it must also be emphasized that the present results are not comparable with those obtained from other records unless they are referred to sternal angle level, or unless the relevant corrections are made.

A number of tracings obtained by direct needle puncture of the left atrium during thoracotomy or bronchoscopy have also been examined. When both are technically adequate, the direct and indirect records in mitral valve disease differ only in respect of the transmission delay of 0·02–0·08 sec. (Epps and Adler, 1953) and the consistently more prominent sound deflections displayed by the latter (Fig. 11). The mean Ry/v values obtained from these direct tracings in four cases of stenosis and eight of incompetence were 1·2 (SD$\pm$0·4) and 2·8 (SD$\pm$1·4) respectively, not significantly different from the indirectly obtained figures, and the form of the diastolic pulse was entirely similar. An example of a direct left atrial pressure tracing in a case of mitral incompetence is shown in Fig. 12.

Good evidence concerning the difference in the rate of y descent in mitral stenosis and mitral incompetence is provided by Fig. 13: this shows the change that took place when incompetence was inadvertently caused by valvotomy (indirect P.C.V.P. tracings). That it is the relief of the obstruction rather than the incompetence which is responsible for the change is shown in Fig. 14, for in this case no incompetence was caused by valvotomy (direct operative tracings).

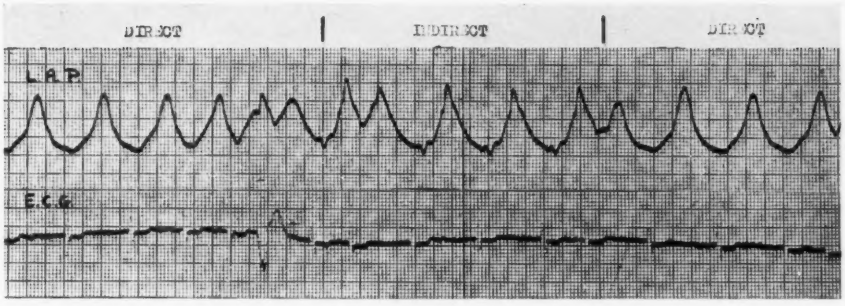

FIG. 11.—Direct and indirect left atrial pressure tracings taken in immediate succession from a case of mitral incompetence (Epps and Adler).

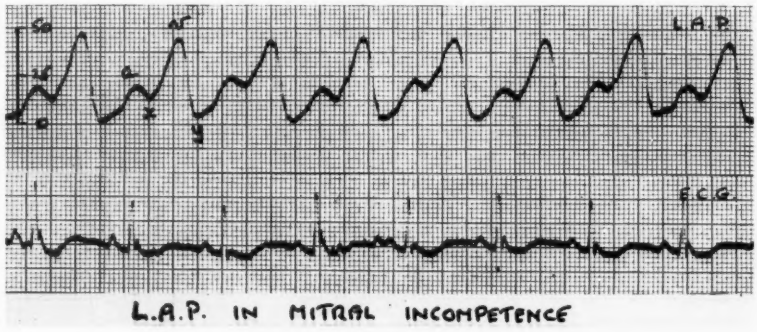

FIG. 12.—Direct left atrial pressure tracing taken at operation in a case of mitral incompetence showing a very rapid *y* descent followed by a diastolic rise of pressure during the latter half of left ventricular filling.

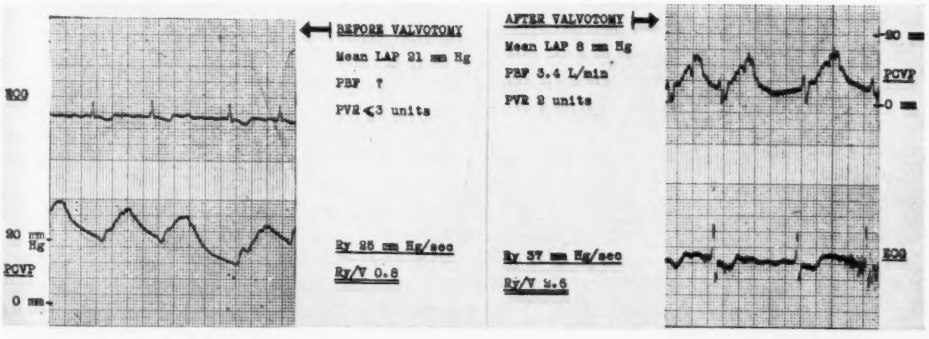

FIG. 13.—Indirect left atrial pressure tracings from a case of mitral valve disease before and after incompetence had been inadvertently induced by valvotomy; the R*y*/*v* ratio rose from 0·8 to 2·6.

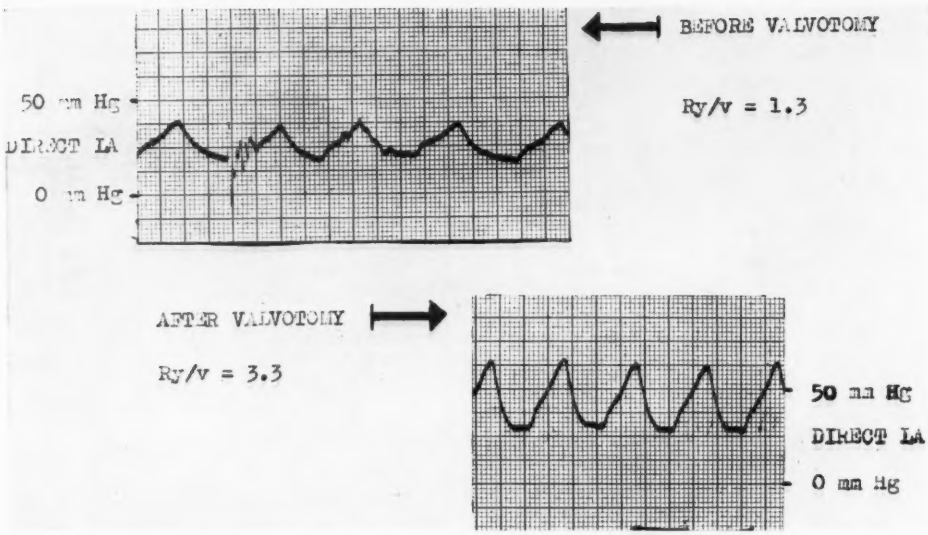

FIG. 14.—Direct left atrial pressure tracings before and after valvotomy in a case of mitral stenosis showing a change in R*y*/*v* ratio from 1·3 to 3·3 after relief of the obstruction.

DISCUSSION

Occasional difficulty continues to arise in correctly apportioning functional significance between stenosis and incompetence of the mitral valve (Baker *et al.*, 1952); clinical evidence may fail to put the issue beyond doubt and assistance must then be sought from right heart catheterization. Despite the intense interest the problem has aroused, the value of this investigation has, however, remained uncertain, and no clearly defined criteria for separating stenosis and incompetence by means of indirect left atrial pressure records have emerged. Attention has centred on the systolic phase in these records: the correlation of high amplitude *v* or systolic waves with regurgitation has been denied (Eliasch, 1952; Biörck *et al.*, 1953; Logan and Turner, 1953; Venner and Holling, 1953) as often as it has been asserted (Lagerlöf and Werkö, 1949; Dexter *et al.*, 1950; Gorlin *et al.*, 1952; Wade *et al.*, 1952), a difference of opinion which accords with the present findings that the relationship has little diagnostic value. Nor has analysis been aided by the presence of sinus rhythm, since pure mitral stenosis is as likely to be associated with a dominant systolic as with a dominant presystolic deflection (Wood, 1954).

Elucidation of combined lesions is further complicated by the disparity between calculated cardiac output and mitral valve flow in the presence of incompetence. Since the Fick output then represents an unknown fraction of actual atrio-ventricular flow, hydrodynamic calculation of valve area (Gorlin and Gorlin, 1951) yields falsely low values imitating stenosis; other and simpler expressions of the relationship between cardiac output and mean atrial pressure (Silber *et al.*, 1951; Werkö *et al.*, 1953; Wood, 1954) and that derived from the output alone (Ravin *et al.*, 1952) are similarly invalidated. In such cases, moreover, the observed mean left atrial pressure diverges still farther from the true diastolic pressure head. However formulæ and data are manipulated, no estimate of the amount of regurgitant flow is possible unless both the fact of regurgitation and the forward area of the mitral orifice are already known (Gorlin and Dexter, 1952), conditions implying autopsy or cardiotomy: such calculations have therefore only an academic interest.

The results of the present study suggest that an expression of the resistance to diastolic flow

imposed by the mitral valve may be derived directly from the atrial pressure pulse. If this suggestion is confirmed, then this constant will possess the important advantage of being neither less accurate nor less valid in the presence of regurgitation since the pressure/flow relationship is not thereby altered (Gorlin, 1953). It may therefore be expected to separate stenosis and incompetence on the basis of their differing forward areas, since both theoretical considerations (Gorlin *et al.*, 1952) and recent experience (Wood, 1954) suggest that severe mitral incompetence and more than mild mitral stenosis are mutually exclusive.

Theory predicts that the rate of blood flow through a stenotic valve orifice will vary not linearly but as the square root of the pressure gradient across it (Rodrigo, 1953); and this relationship has been confirmed in patients with mitral stenosis (Gorlin and Gorlin, 1951). Were the rate of atrial diastolic pressure fall itself a linear function of mitral valve flow rate, the empirical conclusion that Ry/v tends to remain constant would be surprising. No information about the volume-elasticity characteristics of the human left-atrial—pulmonary-venous system is available, but Little (1949) has shown that in dogs pressure is linearly related to values only while it remains in the normal range; when this is exceeded, the rises in pressure in response to constant increments in volume become progressively greater (Fig. 15). If a similar situation is assumed to obtain in man

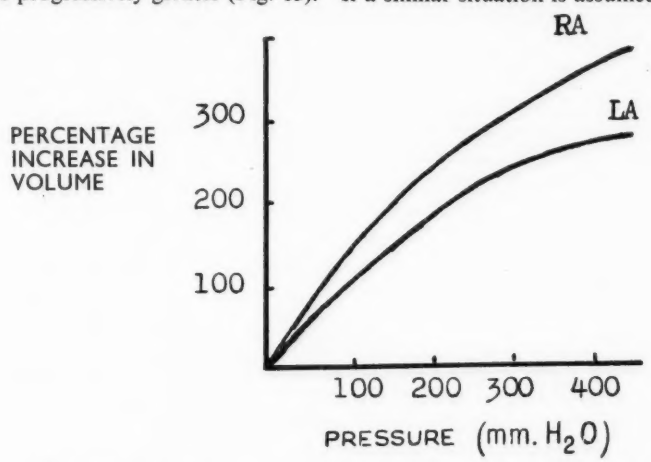

FIG. 15.—Pressure volume curves for right and left atria in dogs (after Little, E. C., 1949; *Amer. J. Physiol.*, **158**, 237).

under the conditions imposed by mitral valve disease, it follows that the ratio of pressure change to volume change will increase as the pressure level rises. The resultant effect will be to approximate the Ry/v ratio to linearity.* That this is in fact the case is suggested by the influence of pressure fluctuations on Ry/v: in face of a rising pressure, if it does not remain absolutely constant, then it may alter slightly in *either* direction.

While these considerations rationalize the observed stability of Ry/v, it follows also from them that the magnitude of the ratio will be influenced by the volume elasticity coefficient of the left atrial system and that it will depart from a sole expression of orifice area to the extent of such influence. The importance of this is at present uncertain; but the high correlation of the ratio with group classification in the present study suggests that it may not be great. It is clear from comparing radiological size of the left atrium with mean atrial pressure in cases of mitral valve disease, that volume-elasticity characteristics are by no means constant from individual to individual.

* If $Ry\sqrt{MVF} \propto \sqrt{v}$ (where MVF=mitral valve flow rate)
then since $MVF \propto \sqrt{v}$, it follows that $Ry/\sqrt{v} \propto \sqrt{v}$
That is, $Ry \propto v$

That anomalous deviation of Ry/v may occur as a result of wide variations in this respect remains an unexcluded possibility (patient N 247 may represent such an anomaly). A firm conclusion as to whether this factor will invalidate finer quantitative application of the ratio must await the accumulation of data adequate to determine its true correlation with orifice area: the present results (Tables III and IV) do not deny that such correlation may be good.

In none of the cases analysed was the mean left atrial pressure less than 8 mm. Hg above the sternal angle. It is unlikely that the conclusions would prove transferable to normal records, since not only is the Ry/v ratio the numerical expression of an abnormal situation, but it is dependent on that situation for its correlation with the pressure/flow relationship across the mitral valve. From the observations of Little already quoted, it follows that Ry/v is not normally a constant since it will still vary with the rate of flow. Under normal conditions, too, small deflections and disproportionately large sound artefacts imply considerable inaccuracy of measurement, while the supposition that the height of v was related to the pressure-gradient would involve a further large error. These considerations are reinforced by the doubt that exists as to the validity of wedged pulmonary arterial records when pulmonary venous pressure is not raised (Epps and Adler, 1953). The use of the word " normal " has therefore been avoided in referring to the Ry/v ratio, and no attempt has been made to establish a normal range of values for the expression.

Conclusions

The limitations of this study are realized, especially that imposed by the relative lack of surgical data from cases of frank mitral incompetence. It is possible that in this group the bias of catheterization records towards borderline and doubtful cases has not been entirely eliminated. Progress in surgical treatment will enable appropriate extension of observations. At present, it may be concluded that the pattern of the left atrial pressure pulse during diastole is determined by the presence and degree of mitral stenosis. With reservations in respect of the excluded outlying observation and the possible influence of varying volume-elasticity characteristics, the Ry/v ratio appears to provide a useful expression of this pattern.

Summary

An attempt has been made to correlate the form of the indirect left atrial pressure record in mitral valve disease with the presence and relative importance of stenosis and incompetence respectively. In pure or dominant stenosis, the time taken for inscription of the y descent is significantly prolonged. The most stable expression of this proved to be the quotient of the calculated rate of fall (mm. Hg per sec.) divided by the height of the preceding v wave (mm. Hg above the sternal angle), the value so obtained remaining relatively independent of individual fluctuations in mean pressure and diastolic length. It is suggested that when the left atrial pressure is raised, this simply calculated ratio varies as the pressure-flow relationship across the mitral valve. On the basis of the results reported, a value greater than 1·6 is unlikely to occur if stenosis is pure or associated with only trivial incompetence. While such a value is not in itself positive evidence of mitral incompetence, it may become so under appropriate clinical circumstances by denying the existence of a significant degree of stenosis.

We should like to thank Dr. J. F. Goodwin and Dr. Walter Somerville for allowing us to inspect some of their intracardiac pressure tracings, Sir Russell Brock and Mr. W. P. Cleland for their co-operation in respect of direct left atrial pressure tracings, and the cardiological technicians at the National Heart Hospital and the Brompton Hospital, particularly Mr. Brabrook-Norman and Mrs. Milne, for their invaluable technical help.

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AORTIC STENOSIS

A POST-MORTEM CINEPHOTOGRAPHIC STUDY OF VALVE ACTION

BY

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In a previous communication (McMillan *et al.*, 1952) we described a method of studying the behaviour of aortic and pulmonary valves post-mortem in an apparatus designed to simulate the natural conditions of pulsatile flow. In this way a photographic record is obtained of the action of normal and abnormal valves and the effects of surgical procedures can be evaluated.

Aortic valvotomy has been performed in this country and in the United States for the last two years (Bailey, 1950, 1952, 1954; Brock, 1954; and Logan and Turner, 1954). The object of this communication is to present the information obtained by this method which is relevant to the selection of cases for this operation.

Method. The apparatus described in the previous paper has been considerably improved (Fig. 1). Water was found to be the most satisfactory perfusion fluid for photographic purposes. The water is pumped from a reservoir (fluid tank) to the heart via a solenoid magnetic valve (1 inch diameter) which allows a continuous flow of about 25 litres a minute or a pulsatile flow of 10–12 litres a minute by the method previously described. After passing into the ventricle and up through the aortic valve, the water is led through a compressible rubber tube, which in conjunction with an air chamber (similar in principle to that used in the standard Starling heart-lung machine, Knowlton and Starling, 1912) allows variations in out-flow and elastic resistance. The water then returns via a rotameter to the reservoir.

In this way the aortic valve can be perfused at a flow equivalent to that in life. The photography is as previously described. It must be emphasized that the results recorded are based on studying the working specimen and cinefilms made from it, and only a few stills taken from them have been used as illustrations.

RESULTS

Fig. 2 shows one cycle of a normal valve. Thirty specimens of stenosed aortic valves have been studied. Each specimen has been placed in the machine and, if the data were available, exposed to conditions as near as possible to those obtaining in life. During continuous and pulsatile flow the valves were studied and photographed. In some cases pressures were recorded with a Sanborn electromanometer, above and below the valve, and in a few cases the valve orifice was measured. The first pressure corresponds to the aortic and the second to the left ventricular pressure.

Attempts were made to split the commissures as far as the aortic wall. When the maximum possible split had been obtained, the specimens were studied again. Of the 30 specimens studied only 3 were not calcified. The distribution of calcification varied from small spicules to large masses and the ability to split the commissure depended directly on the amount of calcification

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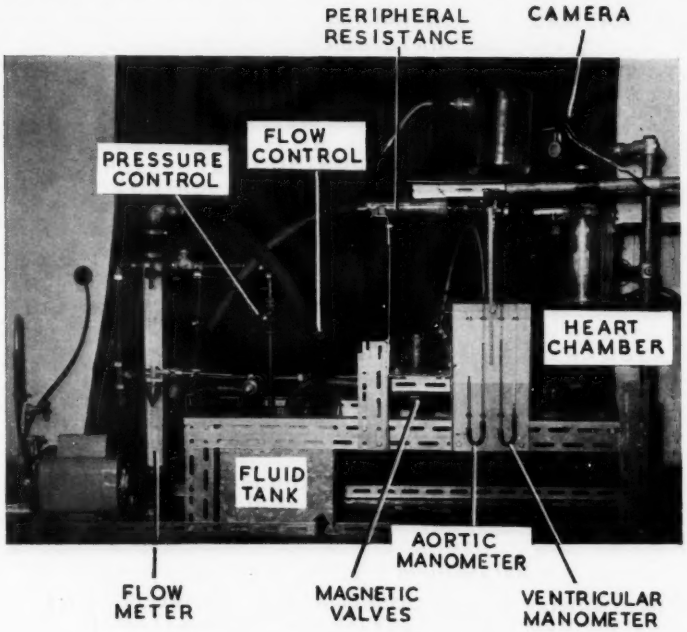

FIG. 1.—The apparatus used for studying heart valve function.

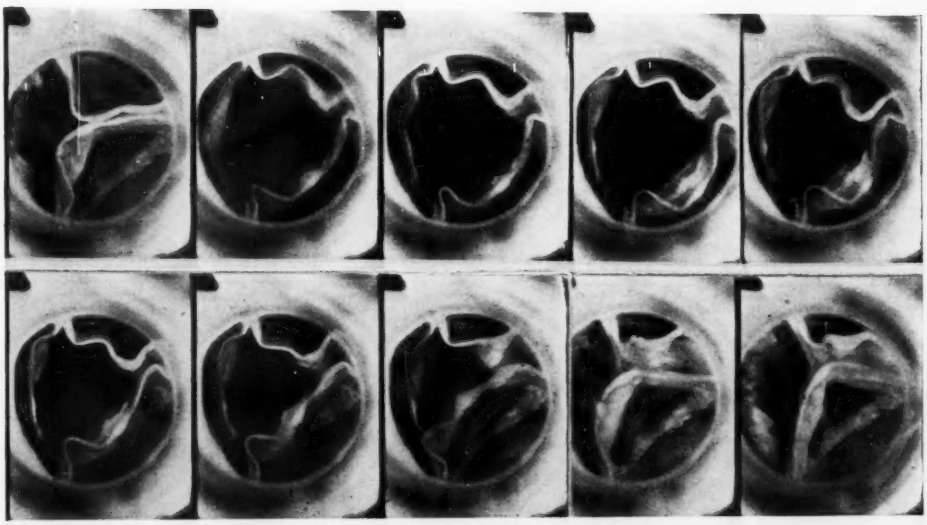

FIG. 2.—A cycle of normal aortic valve movements showing the opening and subsequent closure.

present as it was usually densest in the region of the commissure. Of the three fibrous valves, one had early peripheral commissural fusion with little stenosis (Fig. 3), while the second had severe eccentric stenosis (Fig. 4), and the third central stenosis with all commissures fused (Fig. 5).

Six specimens were examined after the patient had had an aortic valvotomy in life but had died shortly afterwards.

The shape of the orifice varied in every case, but fell into certain groups.

(1) Early peripheral fusion with good function centrally (3 cases) .. Fig. 3
(2) Peripheral calcification not affecting function (1 case) .. .. .. Fig. 6
(3) Fusion of one commissure (14 cases) .. .. Fig. 7 and 11
(4) Partial or complete fusion of two commissures (5 cases) .. .. Fig. 8
(5) Partial or complete fusion of three commissures, often with incompetence (5 cases) .. .. Fig. 9
(6) Cone-shaped valve with an ellipsoid orifice at the apex, and no sign of former commissures (2 cases) .. .. Fig. 10

Types 1 and 2 were presumably degenerative and were accompanied by severe atheroma of the ascending aorta. In Type 3 one-quarter were rheumatic and the ætiology of the remainder was unknown. Types 4 and 5 usually had an associated mitral valve lesion and were presumed to be rheumatic. The type in some cases depended on the ætiology and Type 6 was usually considered to be congenital and known to be in the specimen shown in Fig. 10. This was very difficult to split and was comparable to the cone-shaped congenital pulmonary valve.

Results of Valvotomy Post Mortem

In the first fibrous case (Fig. 3) the lesion was not clinically detectable and no treatment would have been required, in the second (Fig. 4) one commissure split easily with the finger and the other with the knife, and in the third (Fig. 5) they split easily with the Bailey dilator. If these last two cases could have been accurately diagnosed in life, a very good surgical result would have been possible as in the first the flow through the valve increased from 1·9 to 5·5 litres after valvotomy and the pressure difference across the valve decreased from 70 to 20 mm. Hg.

The results in the calcified valves were on the whole disappointing, as in most cases there was considerable calcification in the fused commissures and even if a split was made with a knife, the rigidity of the valves was such that neither movement nor flow were greatly increased (Fig. 8). If an elective valvotomy could be performed on the commissure mainly affected a good result could be achieved (Fig. 11).

Fig. 3.—Peripheral fusion. (a) and (b) Open and shut.
Fig. 4.—Fibrous fusion with excentric stenosis. (a) and (b) Open and shut. (c) and (d) Open and shut after post-mortem valvotomy.
Fig. 5.—Fibrous fusion with three commissures fused. (a) and (b) Open and shut. (c) and (d) Open and shut after post mortem valvotomy.
Fig. 6.—Peripheral calcification, not affecting function. Shut.
Fig. 7.—Bicuspid valve, heavily calcified. (a) and (b) Open and shut.
Fig. 8.—Aortic stenosis and incompetence with one normal and two fused commissures. (a) and (b) Open and shut. (c) and (d) After post-mortem valvotomy showing immobility of divided commissure.
Fig. 9.—Aortic stenosis and incompetence with three commissures fused (a). (b) Showing no improvement after valvotomy.
Fig. 10.—Congenital aortic stenosis. (a) and (b) Open and shut.
Fig. 11.—Bicuspid aortic stenosis. (a) and (b) Open and shut. (c) Showing good result of elective post-mortem valvotomy.
Fig. 12.—Bicuspid aortic stenosis after valvotomy in life (split at lower right-hand corner). (a) and (b) Open and shut.
Fig. 13.—Calcific aortic stenosis after valvotomy in life. (a) and (b) Open and shut. (c) and (d) With Bailey dilator *in situ*, open and closed. (e) and (f) Showing result of post-mortem valvotomy with Bailey dilator.
Fig. 14.—Normal mitral valve seen from left auricle with aortic cusp on right. (a) and (b) Open and shut.
Fig. 15.—Calcific mitral stenosis with aortic cusp on right. (a) and (b) Open and shut. (c) and (d) After post-mortem valvotomy to show optimal result.
Fig. 16.—Aortic stenosis and incompetence with rough edges of the valve. (a) and (b) Shut and open.

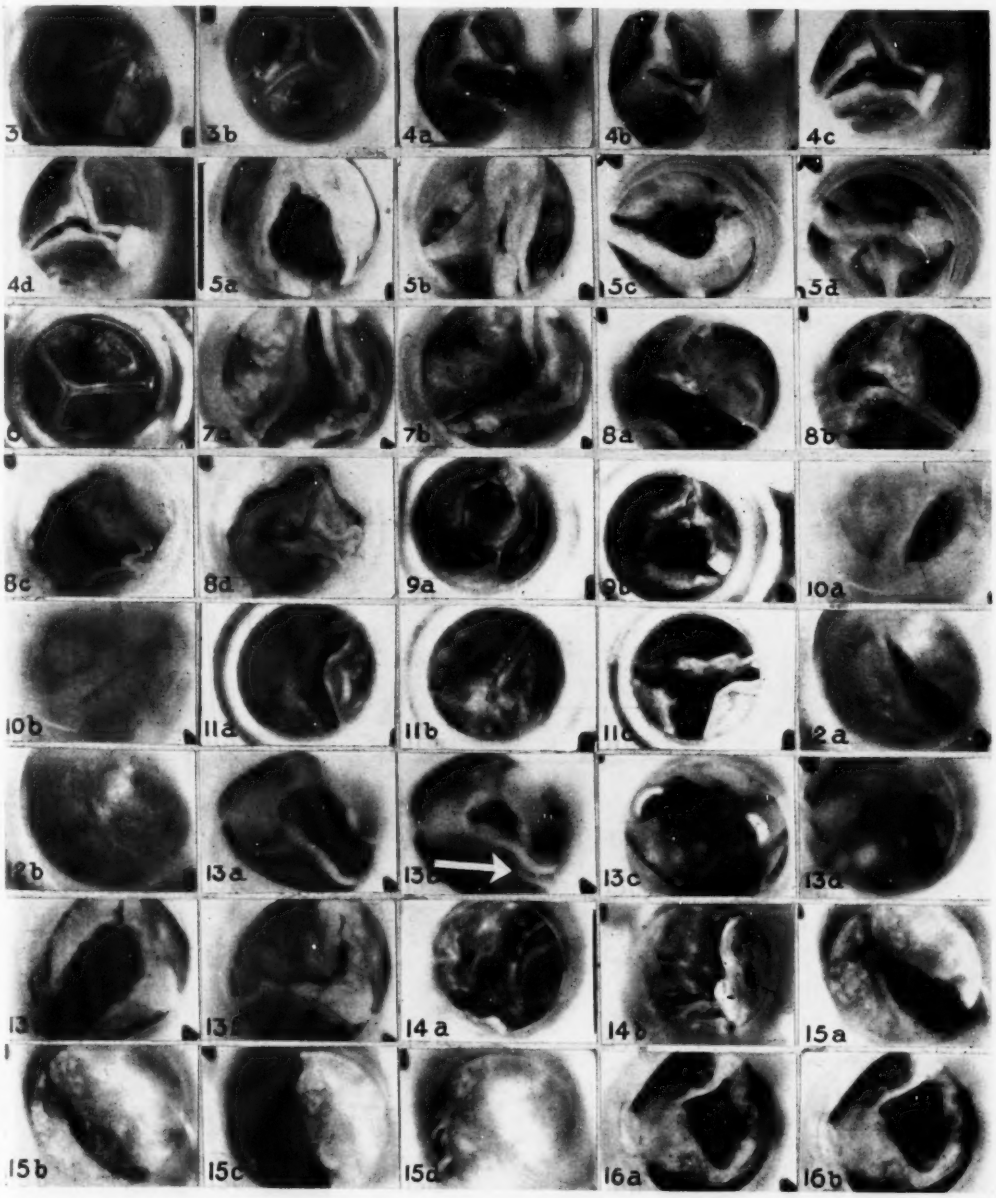
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Fig. 12 shows the effect of dilating a bicuspid valve in life. Here the fused commissure has split to the aortic wall and some mobility has been restored.

Insertion of a dilator either produced no commissurotomy, or splitting of one or two of the commissures, but in no instance was a tri-radiate split obtained by dilation. Selective splitting of the third commissure was only possible with the knife, a method as yet impracticable in life. Fig. 13 shows that with the Bailey dilator (Bailey, 1954) results can be very disappointing, as this specimen had a valvotomy in life. It also shows the Bailey dilator in the same calcified valve performing valvotomy post mortem (c and d) and the results of its action after full opening (e and f). In no case was a calcified valve split except in the region of the commissure. But if one commissure was normal and the rim of the cusp soft, this latter was seen to tear in several cases rather than the calcified area split (indicated by the arrow in Fig. 13b).

Fig. 5 shows a fibrous valve, and an optimal result after post-mortem valvotomy with a Bailey dilator. Fig. 8 shows calcification on one side and mobility on the other. Here splitting of one commissure helped a little but as the calcification occupied half of the fused cusps, attempted dilatation through the pliable part merely pushed the solid part laterally without splitting any further.

TABLE OF RESULTS OF AORTIC VALVOTOMY

No.	Valve type	Calcification	Valvotomy	Result
1	Bicuspid	++	1 commissure	Poor
2	,,	+++	,,	No record
3	,,	+++	,,	Some improvement
4	,,	+	—	
5	,,	++	1 commissure	No improvement
6	,, (Fig. 8)	+++	,,	Slight improvement
7	,, (Fig. 11)	+++	,,	Good
8	,, (Fig. 7)	++	—	
9	,,	+++	—	
10	Congenital bicuspid	+++	1 commissure	Much improvement
11	Bicuspid	++	—	
12	Round hole (Fig. 16)	+++	—	
13	,,	+++	—	
14	,, (Fig. 9)	+++	3 commissures	No improvement, increased incompetence
15	,,	++	—	
16	,,	++	—	
17	1 commissure normal—2 partly fused	+++	—	
18	,, ,,	++	(*a*) 1 commissure split (*b*) 2 commissures split	Slight improvement No further improvement
19	,, ,,	++	—	
20	2 commissures completely fused; 1 normal (Fig. 4)	0	2 commissures	Much improvement
21	Partial fusion 3 commissures	+	—	(Fig. 3)
22	Partial fusion 3 commissures and incompetence	0	—	
23	Peripheral calcification but no fusion (Fig. 6)	+	—	
24	1 commissure completely fused; 2 partly (Fig. 5)	0	2 commissures split with Bailey dilator	Much improvement
			Commissurotomy during life	
25	Bicuspid	++	in vivo	No split
26	,, (Fig. 12)	++	,,	Small split
27	,,	+++	,,	Fair
28	Congenital, cone-shape	+	,,	Minimal split
29	,, ,, (Fig. 10)	++	,,	,, ,,
30	2 commissures completely fused; 1 normal (Fig. 13)	++	,,	Little improvement

Discussion

Leonardo da Vinci (1513) first demonstrated that the normal aortic valve opened to give a triangular orifice and this has been amply confirmed (Fig. 2). It follows, therefore, that the normal orifice is considerably less than the cross-sectional area of the aorta: this is approximately 5·3 sq. cm. (Quain) and the calculated area of the triangle is 2·6–3·5 sq. cm. approximately.

This in practice means that as long as the free borders of the cusps are mobile and shut well, there may be considerable calcification in the peripheral parts of the cusps and walls of the sinuses of Valsalva without limitation of flow in the valve area (Fig. 6). It may be difficult to distinguish the various sites of calcification on radiological evidence alone.

Some fusion of the peripheral parts of the commissures can occur without causing symptoms (Fig. 3). The maximum aortic orifice is much greater than the normal requirement and this combined with the compensatory hypertrophy of the left ventricle provides an explanation for the advanced pathological change often seen post mortem compared with a relatively short disability. It is intended to present data on the critical orifice size and their pressure relationships elsewhere.

Experience with mitral valvotomy suggests that the bivalve structure of the mitral valve can be split with the finger or knife even when calcified (Fig. 14 and 15). But the surgeon has the inestimable advantage of being able to feel the valve and know where the commissures should be, whereas aortic valvotomy at present has to be done blindly by an instrument, so that chance plays a bigger part in deciding the site of the valvotomy. The aortic approach is an advance but the finger can only guide the instrument to the orifice and not select the commissure to be split (Brock, 1950; Bailey, 1954). As mentioned previously valvotomy usually splits the weakest commissure and rarely more than two commissures. In some cases the valve may have been a congenital bicuspid type with a fused raphe representing the third commissure, but even where three commissures were present the third was very difficult to split.

The ventricular approach, however, is the one most commonly used. Attempted blind dilatation of a calcified ring from some distance above the valve may lead to a separation of the aortic wall from the calcified valve which may have dire results as was seen in one case. Another disturbing factor was the roughness of the valve surface, even before splitting, with fibrin and calcified particles only loosely attached. This is much worse after splitting in all except the fibrous valves and makes only too obvious the possibility of peripheral systemic embolism as a result of valvotomy (Fig. 16).

Where one commissure is unaffected a relatively normal cusp may be torn and aortic incompetence result. An early degree of this is shown in Fig. 13b and is marked by an arrow. This hazard can only be eliminated by direct palpation or inspection of the valve. Fig. 13f shows how the damage is increased after repeated post-mortem dilatation of the same specimen.

The chances of a recurrence of the stenosis by fusion of the divided commissure would appear to be high owing to their rough edges and frequent limitation of mobility of the cusps due to calcification, even after splitting (e.g. Fig. 8). The best results would be anticipated in fibrous valves without gross calcification. An accurate method of determining the presence or absence of calcification and of its distribution is urgently needed to improve the selection of cases for operation. In patients with much calcification, exploration is worthwhile if the circumstances justify the risk, as a proportion of such patients may have a commissure amenable to splitting, or the calcification may be outside the critical orifice area.

The orifice size, measured from films taken of the valve working under conditions simulating those in life, was smaller than that obtained by direct measurement with the finger. This was due to the fact that the examining finger post mortem can exert a relatively enormous pressure compared to that produced by the contracting ventricle in life. This would account for what appears to be a good split producing a poor functional result and is correlated exactly with the degree of rigidity of the valve and particularly with calcification.

The method as described in this paper gives very useful information in determining valve action and the effect of surgical procedures on the valves, and by cinematography allows permanent

records to be made. This study has been devoted purely to valve function and no attempt has been made to analyse the differences due to differing æiotlogy.

Conclusions

Thirty stenosed aortic valves were studied post mortem in an artificial perfusion system. Of these 27 showed various degrees of calcification.

The effect of post-mortem valvotomy was studied in 25 specimens, and the results of valvotomy in life in a further 6 specimens.

Many valves after valvotomy were still relatively immobile. Usually it was only possible to split one or two commissures, even with tri-radiate dilators. Unlike mitral valvotomy, large increases of valve area were not easily obtained, except in the uncalcified specimens.

When two commissures were fused, forcible dilatation in some instances damaged the remaining mobile cusp. This could lead to the production of incompetence in life.

The uncalcified stenosed aortic valve is the most suitable for aortic valvotomy as it can be easily divided.

A method of direct inspection of the valves is urgently needed to assess operability, as this cannot be done accurately by existing clinical methods.

The presence of gross calcification seriously militates against a successful functional operative result, but the existing methods of determining the degree and distribution of calcification in life are too imprecise to forbid operation if the circumstances justify the risk.

My thanks are due to Professor W. G. Barnard, Dr. Maurice Campbell, Sir Russell Brock, Mr. G. Mason, and Mr. W. P. Cleland for access to the pathological material.

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PALPABLE VENOUS PULSATIONS IN A CASE OF TRANSPOSITION OF BOTH ARTERIAL TRUNKS AND COMPLETE HEART BLOCK

BY

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The case described is one of cyanotic congenital heart disease, with complete A-V block. Pulsations at the same rate as those of the atria, and at rather more than double the ventricular and radial pulse rates, could be easily felt above the clavicles and in the groins. These pulsations were so forcible that they were thought to be arterial in origin by a number of observers. We are of the opinion that they were venous pulsations, arising in the right atrium and reaching the femoral and jugular veins via the venæ cavæ.

Case Report

The patient was 34 years old. Cyanosis had been noted when he was nine months and he had become breathless on slight exertion from the time he could walk. He had been well enough to follow various light occupations until 1944, when at the age of 27, he was admitted to hospital because of melæna. He was found then to have complete A-V block and cyanotic heart disease, thought to be pulmonary stenosis and ventricular septal defect.

Examination showed marked cyanosis, clubbing of the fingers, œdema of the legs, and ascites. The radial and posterior tibial arteries were beating regularly at 44 a minute. Pulsations at 103 a minute, which were irregular in force, were felt in both groins and above the clavicles. The apex beat was in the fifth intercostal space in the anterior axillary line. A systolic thrill was palpable over the whole præcordium. The first heart sound was replaced by a long, loud, harsh systolic murmur, best heard at the pulmonary area, but audible over the whole præcordium. The second heart sound could not be identified. Between the murmurs there were softer and more rapid sounds, thought to be due to atrial contractions. Some murmurs were louder than others, presumably because of atrial and ventricular contractions occurring close to one another. The blood pressure was 155/90. The urine contained albumin (12 parts Esbach). The hæmoglobin was 152 per cent and the red blood corpuscles 9 millions per cu. mm. Examination of the other systems showed nothing of note.

After the signs of congestive failure had cleared, the venous pressure in the right arm was 6 cm. of saline above the manubrium sterni. Pulsations of the same rate and pattern were seen and felt over the jugular and femoral veins at the same rate as the P waves. The left femoral artery and vein were exposed surgically. The artery was seen pulsating at 45 a minute, and the vein, almost as vigorously, at 100 a minute. The mean pressure in the femoral vein was 6 cm. of saline above the manubrium sterni with the patient recumbent, and in the saphenous vein 5·5 cm. The venous pulse pressure could not be measured because of the inertia of the saline manometer, but the vein was observed to bleed in spurts, like an artery. The venous pulsations were therefore of atrial origin, reaching the groins and neck via the venæ cavæ. The waves recorded from the groins varied manifestly in size, and tracings taken simultaneously from the right groin and from the cardiac apex showed that the largest waves in the femoral tracings occurred at about the same time as ventricular contractions, i.e. when the tricuspid valve was closed (Fig. 1, a3, a5, a8, and a10). They were, then, so called " cannon " waves. Either one or two waves occurred between each successive pair of cannon waves. Where two waves occurred (Fig. 1, a1 and a2, a6, and a7) the earlier of the two was always the smaller and this is explained by the atrium contracting early in ventricular diastole, when the ventricular pressure was lower and the tricuspid valve wider open than when the next atrial contraction

occurred towards the end of ventricular diastole. The size of each wave can be related to the stage of the ventricular cycle at which it occurred, the waves increasing in size the later in ventricular diastole they appeared, the largest being during ventricular systole (Fig. 1, a3, a5, a8, and a10).

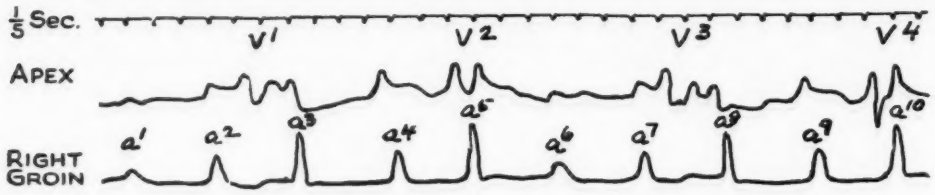

FIG. 1.—Polygraph tracings taken over cardiac apex and right groin (see text).

X-ray examination showed that the heart was markedly enlarged, particularly the right atrium and right ventricle. Electrocardiograms confirmed the presence of complete A-V block. Right axis deviation and tall R waves in leads aVR and V1 to V4 were clear evidence that the right ventricle was greatly hypertrophied.

The patient was treated along the usual lines for cardiac failure and recovered enough to be able to walk short distances. After several further episodes of congestive failure, he was admitted to hospital again some months later in an attack from which he did not recover.

Summary of Post-mortem Findings

Bilateral hydrothorax and extensive collapse of both lungs. Hydropericardium and ascites (500 ml.). Chronic venous congestion of viscera.

The Heart. The pericardial sac contained some 500 ml. of pale greenish transudate and irregular sclerotic patches were noted in the epicardium but, in other respects, the sac was normal. The anterior aspect of the heart *in situ* was trapezoid in shape and the aorta, springing from its upper left angle, arched upwards, backwards, and to the right: the front of the ascending portion of the arch was overlapped by the greatly enlarged auricle of the right atrium which concealed the pulmonary trunk behind it (Fig. 2). The main

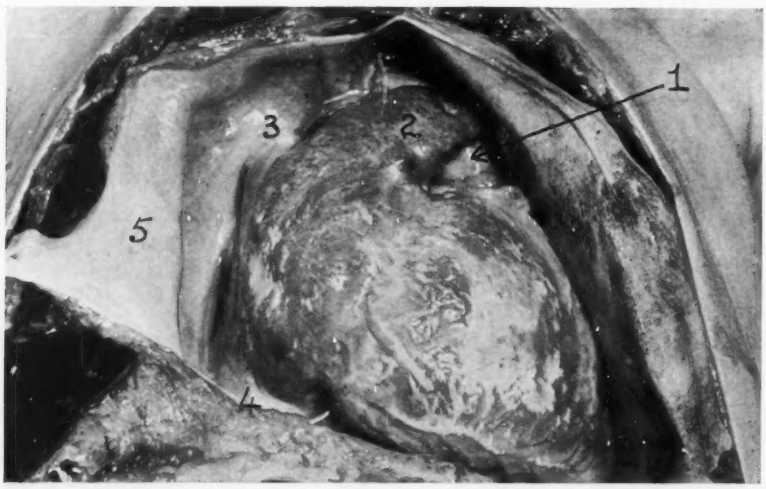

FIG. 2.—The heart *in situ* in the opened thorax. (1) Aorta. (2) Enlarged auricle of right atrium. (3) Superior vena cava. (4) Inferior vena cava. (5) Reflected parietal pericardium.

branches of the aorta were normal in their origin and distribution and the ligamentum arteriosum was impervious. The several measurements recorded below were made on the formalin-fixed heart.

The ventricular portion of the heart was sub-divided into a large conical right-sided chamber and a small concave-convex left-sided chamber by an abnormal septum presenting an arched defect, 20 mm. at the base and 10 mm. high, in its upper and posterior part, through which the two chambers communicated. The left-sided chamber (Fig. 3), measuring 25 mm. from base to apex, 25 mm. from front to back, and 10 mm.

FIG. 3.—Left-sided ventricular chamber: outer wall excised. (1) Aorta. (2) Abnormal septum and base of arched defect. (3) "Anterior" and (4) " Posterior " coronary artery.

in maximum depth near the base, was situated almost exactly in the sagittal plane and gave origin from its base to the aorta; its wall had a maximum thickness of 11 mm. The aortic valve (after restoration of an excised wedge) measured 65 mm. in circumference (normal, 75 mm. in fresh state) and possessed three well-formed semilunar cusps of nearly normal texture, one posterior and two antero-lateral. The right-sided chamber, measuring 90 mm. in internal length from base to apex and 50 mm. in diameter near its base, had a wall of 15 mm. thickness. It was a composite chamber into which both A-V orifices led and from which the pulmonary artery sprang behind and to the right of the aorta (Fig. 4), in a narrow interval between the septal cusp of the right A-V valve and the upper limb of the abnormal septum. The channel of exit from the ventricular chamber into the pulmonary artery (deliberately avoiding the term " infundibulum ") measured only 30 mm. in circumference; its wall was sclerosed by fibrous tissue, representing a pre-valvular stenosis; the circumference of the artery increased to 47 mm. (normal, 72 mm.) at the level of the valve which possessed only two cusps, namely a large anterior and a small left postero-lateral, united near their contiguous margins by a supplementary bridge of fibrous tissue. The right A-V orifice was guarded by a valve with three identifiable cusps, septal, posterior, and anterior, and its axis was directed from above, downwards, and to the left towards the lower limb of the abnormal septum. The left A-V orifice, situated behind and to the right of the tricuspid, was guarded by two cusps, an anterior and a posterior of nearly equal size, and its axis was directed from above, downwards, and to the right towards a pocket, formed by

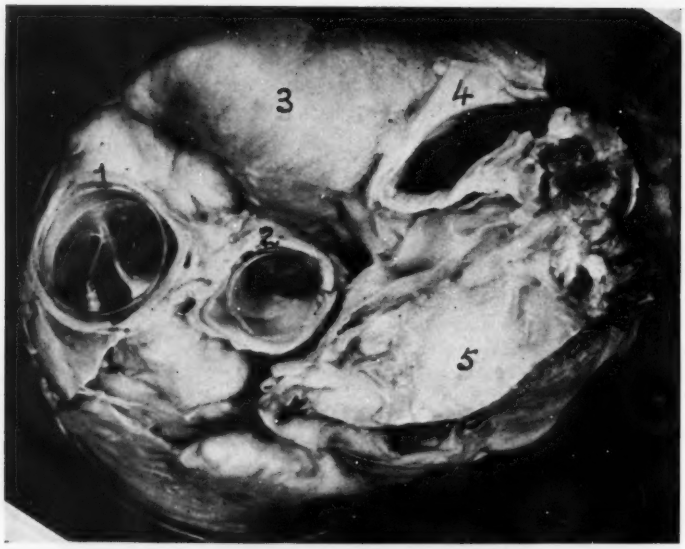

FIG. 4.—Base of heart, viewed from above and slightly behind. The reconstructed and partially collapsed aorta and pulmonary artery are distended with glass rings. (1) Aorta showing right and left anterior cusps. (2) Pulmonary artery showing part of anterior cusp only. (3) Enlarged auricle of right atrium with deep aortic groove on posterior surface near tip (displaced forwards for photographic purposes). (4) Superior vena cava. (5) Left atrium.

the bases of two papillary muscles on the outer (i.e. right lateral) wall of the chamber. The cusps of the bicuspid (mitral) valve were normal in texture but those constituting the tricuspid valve were sclerosed, especially the septal cusp which presented a rounded fibrous polyp, some 5 mm. in diameter, on its atrial surface. The papillary muscles and chordæ tendineæ showed only one notable abnormality, evidenced by the attachment of a thick muscular bundle, derived from the coalescence of two papillary muscles, to the ventricular surface of the anterior cusp of the tricuspid valve. The apical part of the chamber presented prominent columnæ carneæ, mainly disposed in a longitudinal direction, and was crossed horizontally by one conspicuous muscular bundle representing a moderator band. The circumference of the right and left A-V orifices measured respectively 80 mm. (normal, 120 mm.) and 72 mm. (normal, 100 mm.).

The right atrium measured 100 mm. transversely from its right lateral wall to the tip of its auricle and 50 mm. in the vertical plane. Its wall was hypertrophied up to 3 mm. in thickness, exclusive of the unusually prominent musculi pectinati, despite the considerable dilatation of its chamber. The orifices of the superior and inferior venæ cavæ were normal except that the Eustachian valve was not identifiable. The orifice of the coronary sinus was imperforate and the cardiac veins drained into a persistent left superior vena cava. The foramen ovale was patent as a slit-like aperture, 10 mm. in length, guarded by a flap valve on the left surface of the inter-atrial septum. A broad groove on the surface of the posterior wall of the right auricle marked the site of contact with the ascending aorta. The left atrium was situated directly behind the right, slightly to the right of centre; it measured 45 mm. in the transverse and 30 mm. in the vertical plane. Its wall was slightly hypertrophied, up to 2·5 mm. in thickness, and its chamber was dilated but much less than that of the right. The pulmonary veins entered the right and left upper angles of the left atrium in the normal situation.

The coronary arteries, springing one from the right anterior and another from the posterior sinus of Valsalva, had an anomalous distribution and were transposed as described by Spitzer; both were unusually large and tortuous and exhibited patches of atheroma.

Comment. It is not proposed to discuss here the arguments for and against Spitzer's phylogenetic theory of the transposition of the arterial trunks. It is sufficient to say that the heart described above is closely

similar to his Case 9 (1923, pp. 243–253). Indeed it differs only in the respect that " detorsion of the bulb," in Spitzer's phrase, has proceeded still further to the extent that the " aortic chamber " has been carried from the right anterior to the left lateral aspect of the heart. Presumably as a result of this increased " detorsion," the conus of the right ventricle has been compressed, a pre-valvular stenosis of the pulmonary artery has developed, and the pulmonary valve has become bicusped while the aorta, identified by Spitzer as the homologue of the right (reptilian) aorta, receiving an increasing volume of blood through the defect in the abnormal septum, has undergone a corresponding enlargement and has retained three enlarged cusps. The " aortic chamber " is, in fact, a minor segment of a morphologically *right* ventricle, communicating through a defect in an abnormal septum with a major segment of the same which has coalesced with a morphologically *left* ventricle owing to the suppression of development of a normal interventricular septum. No clinical details about Spitzer's Case 9 are reported but he attained adult life like the present patient.

Analysis of the hæmodynamics of a structurally abnormal heart is always hazardous, especially in a fixed organ, but there are some notable findings in this instance which might be significant in the interpretation of the clinical manifestations:

(1) The deviation of the axes of the right and left A-V valves should have effected a partial separation of the venous and oxygenated blood and ensured that the blood entering the pulmonary artery was mainly venous.

(2) Having regard to (*a*) the large capacity of the chamber of the composite ventricle, (*b*) the rigidity of the small exit from it into the pulmonary artery, and (*c*) the comparatively large aperture leading into the " aortic chamber," it is almost certain that the aorta was not only larger than normal but also, perhaps, abnormally distended during each ventricular systole. This proposition is supported by the appearances of the aorta *in situ* (Fig. 2). Therefore, the reduction in the measured circumference (from 75 to 65 mm.) of the reconstituted aortic valve in the formalin-fixed specimen is probably misleading.

(3) The fibrous thickening of the cusps of the right A-V valve would suggest that there had been a moderate degree of stenosis, probably associated with incompetence, during life.

(4) The relatively great enlargement of the chamber of the right atrium and the greater hypertrophy of its wall compared with that of the left would suggest that occasionally at least, if not during every atrial systole, blood was expressed from the right atium into the left through the patent foramen ovale.

(5) The conspicuous groove upon the posterior surface of the greatly enlarged right auricle, where it impinged upon the ascending aorta, admits no reasonable doubt that the pulsation of the aorta was transmitted to the blood contained in the right atrium during every ventricular systole, whether that pulsation was recordable in the peripheral venous circulation or not.

Discussion

Pulse waves synchronous with atrial systole can be demonstrated in the jugular vein in normal subjects, the " a " wave of the jugular phlebogram. Except for the vestigial Eustachian valve, there are no valves between the venæ cavæ and the atrium. Muscular bands thought to close the venous orifices during atrial systole, have been described by Keith (1902). Authorities differ in their explanations of the mechanism of production of the normal " a " wave. Best and Taylor (1950) state that the jugular vein is in direct communication with the interior of the atrium and that changes in volume and pressure in the atrium are transmitted to the column of venous blood. According to Wiggers (1949) the venous channels remain patent and regurgitation of blood into the venæ cavæ is prevented (1) by the necessity of stopping the forward flow before the stream can be reversed, (2) by the pressure being lower in the ventricle than in the veins so that the atria tend to empty in the direction of least resistance, (3) by the peristaltic mode of contraction favouring emptying towards the ventricles, and (4) by the emptying of atria during early (ventricular) diastole so that they contain but a small quantity of blood when they contract.

Wright (1952) explains the " a " wave by a rise in pressure in the great veins, caused by stasis of the blood stream. He states that there is no regurgitation of blood from atrium to veins during atrial systole as the orifices are then closed by the sphincter-like action of sleeves of atrial muscle. Evidence in agreement with this latter view has been recorded by Hedman *et al.* (1953) by rapid angiocardiographic studies: they conclude that the caval orifices are normally closed during atrial systole.

Clinically detectable pulsations in limb veins have been described in cases of relative and absolute tricuspid incompetence, sometimes with varicosity of the veins of the legs (Benson, 1836; Kerr and Warren, 1925; Clerc and Mourrut, 1931; Hallok and Clarke, 1941; and Sensenbach and Hutaff, 1943).

Unusually large atrial (giant " a ") waves may be seen in the jugular venous pulse in severe pulmonary stenosis, pulmonary hypertension, and tricuspid stenosis (Wood, 1950). Visible and palpable presystolic waves were described by Dagnini (1894) in sphygmograms taken from the groins in a case of rheumatic heart disease; he thought that they were of atrial origin and transmitted to the femoral vein and that tricuspid stenosis was present in his case. Pezzi and Gasperini (1914) described similar waves in three cases of congenital heart disease, but these waves do not seem to have been palpable: pulmonary stenosis was present in two of the cases.

Waves at atrial rate are often visible in the jugular pulse in complete A-V block. Kerr and Warren (1925) mention a case in which these waves were seen in the veins of the arms. When the atrium contracts against the closed tricuspid valve the " a " waves are larger than usual and these " cannon " waves are described as abrupt, variable, and of high amplitude (Wood, 1950). In a case of A-V block, without any valvular lesion, Pezzi *et al.* (1920) felt feeble pulsations at atrial rate in the groins, and were able to record these pulsations in sphygmograms taken over the femoral vessels. Webster (1901), Mackenzie (1913), and other authors have described small undulations at atrial rate, between the ventricular waves on the radial arteriogram, in cases of heart block. Mackenzie thought that these waves were produced by left atrial systole causing pressure on the aortic valves and so on the arterial blood column. Hedman *et al.* (1953) in their angiocardiographic studies in a case of complete heart block found regurgitation of contrast medium from atrium into venæ cavæ when atrial and ventricular systoles coincided.

In the case described here, we consider that the contractions of the greatly hypertrophied right atrium overcame the normal mechanism for closing the caval orifices, causing regurgitation of blood into the venæ cavæ and so producing the remarkably vigorous pulsations in the veins of the groins. This would seem to be the mechanism whereby giant " a " waves in the jugular venous pulse are produced in conditions leading to marked hypertrophy of the chambers of the right heart. The fact that the largest of these pulsations in the femoral veins coincided with the ventricular pulsations, and so with closure of the tricuspid valve, indicates a similar causal mechanism for the " cannon " waves of heart block.

In our case the pulsations were unusually evident because of the combination of gross right atrial hypertrophy and complete A-V block. Pulsations of atrial origin may reach the femoral veins more frequently than is recognized. Their presence will be difficult to detect by ordinary clinical examination, except possibly when there is coexistent complete heart block.

Summary

A case of mixed transposition of both arterial trunks, exemplifying Spitzer's Type IV, with complete atrio-ventricular block is described.

Pulsations at the same rate as the atrium were easily palpable in both groins. These pulsations were shown to be occurring in the femoral veins and the mechanism of their production is discussed.

We are indebted to Dr. Douglas Taylor for the polygraph tracing.

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THE MECHANISM AND SIGNIFICANCE OF THE AURICULAR SOUND

BY

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The auricular sound (variously referred to by other writers as the fourth heart sound, presystolic gallop, or auricular gallop) is heard under certain pathological conditions. It is a dull, low-pitched sound, audible along a line joining the apex to the xiphoid, and is usually more obvious at the latter site. It may be heard either with a bell chestpiece or a thin diaphragm, and is appreciated best of all by direct auscultation with the ear on the patient's xiphoid, as described by Potain, when the combination of thrust and sound is very obvious. It may indeed be better felt than heard, since its frequency is too low to be transmitted adequately by stethoscope tubing (Rappaport and Sprague, 1942).

The auricular sound must be differentiated from other additional sounds. Physiological splitting of the first heart sound is recognizable because its two components are high-pitched, whereas the auricular sound is of low frequency. The time interval between auricular and first sounds (0·08 sec.) is greater than that separating the two components of a split first sound (0·03 sec., Wolferth and Margolies, 1931); and splitting varies with respiration, becoming more obvious during expiration. An early systolic ejection sound which may occur with dilatation of the pulmonary artery or aorta (Leatham and Vogelpoel, 1954) is also of high frequency and is clearly audible over the base of the heart. Summation gallop (Wolferth and Margolies, 1933), due to superimposition of the third and auricular sounds, will disappear if the heart can be slowed by carotid sinus pressure, and can be differentiated from the auricular sound by this means.

Previous writers have expressed differing views on the production of the auricular sound and on its prognostic significance, especially in relation to cardiac failure. Since the introduction of multi-channel instruments has now made it possible to record heart sounds and intracardiac pressures simultaneously, it was decided to investigate the relationship of the auricular sound to other events in the cardiac cycle by this means, in order to obtain information about the mechanism of its production. In addition, clinical and phonocardiographic studies were made in a large number of patients to re-assess the significance of the sign.

Methods. Simultaneous sound and pressure recordings were available from 12 cases of congenital heart disease with either pulmonary hypertension or pure pulmonary stenosis in which an auricular sound was present: cardiac catheterization had been undertaken for diagnostic purposes. These tracings were used for direct timing of the auricular sound in relation to pressure changes. They were made with a Sanborn electromanometer and a four-channel recorder designed by New Electronic Products, Ltd.

A clinical study was made of 88 other patients in whom the auricular sound was audible, and a phonocardiogram taken in 62 of them. There were 46 patients with hypertension, 29 with cardiac infarction, 4 with aortic valve lesions, and 9 with heart block. In the hypertensive group there was one patient with coarctation of the aorta and another with chronic nephritis. The remaining 44 had essential hypertension and three of these were seen during a malignant phase. Six of the patients with infarction were studied within a few days of the acute attack, and the remainder at periods varying from three months to several years after; in all cases there was electrocardiographic confirmation.

The clinical, electrocardiographic, and radiological findings in these 88 patients were compared with those in 205 with similar diseases in whom the auricular sound was not detected. In this group there were

86 patients with hypertension (including five with coarctation of the aorta), 16 with recent and 62 with old cardiac infarction (with electrocardiographic confirmation), and 42 with pure aortic valve lesions, cases with co-existent mitral disease being excluded. In addition, over 100 adults with no evidence of cardiovascular disease were examined to find out if the auricular sound was ever audible in health. All patients were examined by the author.

The majority of phonocardiograms were obtained with amplifiers and string and mirror galvanometers made by the Cambridge Instrument Co. The medium frequency channel (Leatham, 1952) corresponds approximately to the findings on auscultation with the bell type of stethoscope or with a thin diaphragm, and was found suitable for recording the auricular sound. (The low frequency record shows it even more clearly, but also shows vibrations that may be inaudible.) The high-frequency record ("logarithmic" of Rappaport and Sprague) corresponds more closely to auscultation with the conventional diaphragm, but so attenuates the low-pitched sounds as to be of no value in this study. In all cases, phonocardiograms were recorded from the mitral area and the lower left sternal edge simultaneously with lead I or lead II of the electrocardiogram. In this investigation, vibrations starting after the onset of the P wave of the simultaneous electrocardiogram were considered to be of auricular origin only if their onset preceded that of the QRS complex, so as to avoid confusion with the muscular component of the first heart sound described by Rappaport and Sprague (1942).

Mechanism of the Auricular Sound

Recordings from patients with heart block demonstrate the features of auricular contraction uninfluenced by succeeding ventricular events. When separate auricular sounds were not heard, a group of small vibrations were seen on low-frequency traces, following the P wave of the cardiogram (Fig. 1). These were below the range of audibility (Rappaport and Sprague, 1942). In

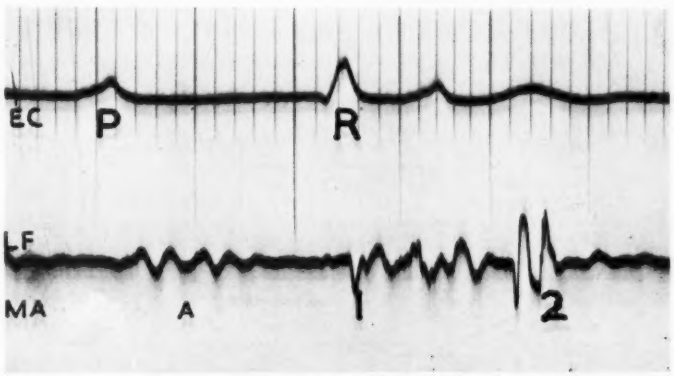

Fig. 1.—Low amplitude auricular vibrations (A) in a case of complete heart block, in whom no auricular sounds were audible.

(In this and in subsequent figures, EC or II denote the electrocardiogram, MA indicates mitral area (apex), LSE lower left sternal edge, MF and LF medium and low frequency channels respectively, and A, I, and 2 show auricular, first, and second heart sounds.)

cases with audible auricular sounds the later vibrations of the group were greatly increased in amplitude so that the auricular vibrations appeared to be in two sets (Fig. 2). This "double" appearance of the auricular sound in recordings from cases of heart block has previously been noted by McLeod *et al.* (1932), Duchosal (1932), Braun-Menendez (1938), and Evans (1943). This intensification of the later auricular vibrations was a constant feature of phonocardiograms recorded from patients with audible auricular sounds, irrespective of the actual cardiac lesion present. Their relation to electrical and mechanical events in the right heart are shown in Table I.

The earlier, inaudible component of the auricular vibrations corresponds in timing to the rise of pressure in the right auricle, while the audible component does not occur until 0·05–0·09 sec.

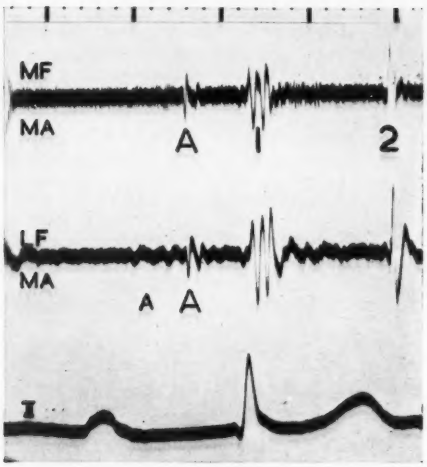

FIG. 2.—Inaudible (a) and audible (A) components of auricular sound.

TABLE I

TIME INTERVALS IN 12 PATIENTS CATHETERIZED BECAUSE OF PULMONARY HYPERTENSION OR PURE PULMONARY STENOSIS

Onset of P wave to onset of early auricular vibrations	0·09 sec. (0·08–0·10)
Onset of P wave to onset of late (audible) auricular vibrations	0·12 sec. (0·09–0·16)
Onset of P wave to onset of right auricular systole	0·06 sec. (0·05–0·07)
Onset of right auricular systole to audible auricular vibrations	0·07 sec. (0·05–0·09)

later. These findings indicate that the audible component is a filling sound produced by blood entering the ventricle from auricular systole, while the preceding inaudible vibrations are due to the actual muscular contraction of the auricle. This view is in keeping with the experimental work of Wiggers (1949), who showed that the maximum increase in ventricular volume occurs later than the maximum rise in auricular pressure: and of Braun-Menendez and Solari (1938) who recorded two groups of auricular vibrations in dogs. They too considered these to be produced respectively by auricular contraction and ventricular filling.

While no direct comparison with pressure records from the left heart was available, the relationship between electrical and phonocardiographic events was found to be similar to that already described (see Table II).

The average interval between the onset of the P wave and the onset of the early auricular vibrations was 0·12 sec. A similar time interval was found between the onset of the P wave and the onset of left auricular contraction (as shown by the " a " wave in direct tracings from the left auricle) recorded by cardiac catheterization in eight cases of auricular septal defect. This supports the view that the early vibrations are produced by auricular contraction. The larger, audible vibrations

occurred 0·05–0·11 sec. later, and so could be produced by filling of the left ventricle. The onset of left auricular vibrations occurred 0·03 sec. later than the right side and this is in keeping with the work of Groedel (1948), who showed that activation of the left auricle took place 0·03 sec. after the right. The duration of the whole group of auricular vibrations was found to range from 0·04 to 0·14, with an average of 0·095 sec.

TABLE II

RELATION OF AURICULAR VIBRATIONS TO ELECTROCARDIOGRAM IN LEFT-SIDED LESIONS

	Onset of P wave to onset of early auricular vibrations	Onset of P wave to onset of audible auricular vibrations
Hypertensive heart disease (29 recordings)	0·125 sec. (0·08–0·16)	0·17 sec. (0·14–0·24)
Cardiac infarction (21 recordings)	0·10 sec. (0·07–0·15)	0·17 sec. (0·12–0·20)
Aortic valve disease (4 recordings) ..		0·18 sec. (0·16–0·23)
Heart-block (8 recordings)	0·12 sec. (0·09–0·15)	0·21 sec. (0·16–0·25)

Similar values for these time intervals and for the duration of the sound have been recorded by other observers (Wolferth and Margolies, 1933; Lewis, 1934; Duchosal, 1935; and Miles, 1951). These authors, however, did not make a clear distinction between audible and inaudible components.

There was no obvious respiratory variation in the amplitude of the audible component in most of the tracings in the present series. In a small number it became larger during inspiration (Fig. 3), but this was not appreciable by clinical auscultation.

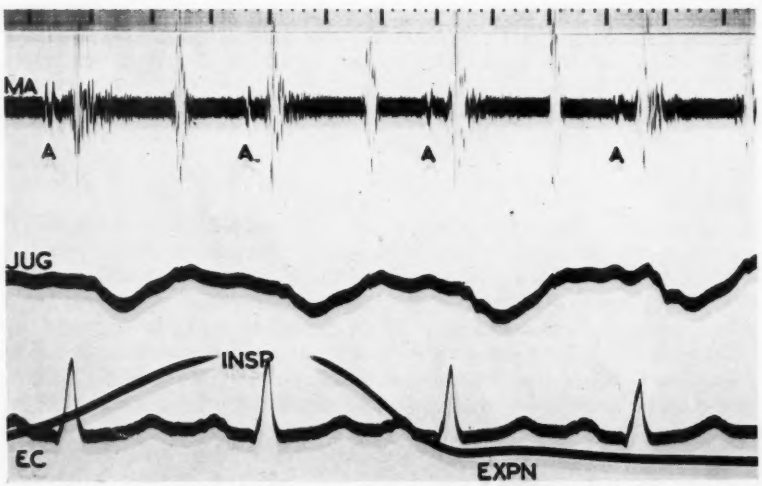

FIG. 3.—Increased amplitude of auricular sound (A) during inspiration. JUG=jugular venous pulse.

The Auricular Sound in Hypertension

The findings in patients with hypertension are set out in Table III. Electrocardiographic or radiological evidence of left ventricular hypertrophy was present in 44 of the 46 cases with an auricular sound; in the remaining two the electrocardiogram showed ischæmic changes. The sound was never detected in any patient when both X-ray and electrocardiogram were normal.

TABLE III

Findings in 131 Hypertensive Patients

		With auricular sound (46 patients)	With no auricular sound (85 patients)
Condition of left ventricle	Hypertrophied	96%	75%
	Normal size with ischæmic EC.	4%	5%
	Normal	0	20%
Functional capacity of patient	Failure—Congestive	9%	6%
	Failure—Left ventricular	14%	3%
	Total	23%	9%
	Effort dyspnœa	23%	33%
	Anginal pain	34%	25%
	Symptom-free	20%	33%
Blood pressure	Average	210/125	200/120
	Range	290–160 100–110	290–150 150–110

It should, however, be noted that left ventricular hypertrophy was present in 75 per cent of patients without an auricular sound, and was not necessarily any less marked (see also Miles, 1951). The incidence of cardiac failure was higher (23%) in the group with the sound, than in those without (9%), but the majority of patients were ambulant and 20 per cent of the patients with the auricular sound were symptom-free. Blood-pressure readings in the two groups showed no significant difference and the age distributions were also similar.

The Auricular Sound in Cardiac Infarction

The auricular sound was heard in 6 of 22 patients with recent cardiac infarction. No influence on immediate prognosis was noted in this small series. (In a larger, unpublished series of 176 cases of recent infarction admitted to the National Heart Hospital but not all examined by the author, data from the case-records showed a higher mortality and greater incidence of cardiac failure when the auricular sound was heard.) In the present series the sound was still present after recovery in 23 patients and persisted throughout the period of observation. Nine of these patients had hypertension and were excluded from the analysis because of this additional ætiological factor. Table IV sets out the findings in the 54 cases with normal blood pressures who were observed after recovery from the acute attack.

It will be seen that the incidence of cardiac failure was much higher among patients with the auricular sound (36%) than in those without (2·5%). Limitation of effort from this cause in the cases with an auricular sound accounts for the low incidence of effort pain in this group. Radiological enlargement of the left ventricle was present in a high proportion of this group, but was

TABLE IV

FINDINGS IN 54 CASES OF CARDIAC INFARCTION WITH NORMAL BLOOD PRESSURES, AFTER RECOVERY

		With auricular sound (14 patients)	With no auricular sound (40 patients)
Left ventricular enlargement		80%	42%
Functional capacity of patient	Failure—Congestive	28%	2·5%
	Failure—Left ventricular	8%	0
	Total	36%	2·5%
	Effort dyspnœa	20%	20%
	Anginal pain	28%	62·5%
	Symptom-free	16%	15%
Extent of infarction	Extensive	25%	16%
	Localized	75%	84%
Blood pressure	Average	130/80	130/80
	Range	160–100 90–60	160–100 90–60

absent in 20 per cent. Extensive changes in the electrocardiogram were found in 25 per cent of the patients with the sound, as against 16 per cent in those without. There was no significant difference in blood pressure readings or in the age distribution in the two groups.

THE AURICULAR SOUND IN OTHER CONDITIONS

The auricular sound was heard in 4 of 46 patients with aortic valve disease. It was found in 3 of 23 cases with pure or dominant stenosis and in 1 of 23 with pure or dominant incompetence. In all four the electrocardiogram showed left ventricular hypertrophy: this was found in all but 3 of the 46 cases.

No detailed study was made of the incidence of the sound in congenital heart disease; the 12 cases in this series served principally to provide information about the timing of the auricular sound in relation to auricular systole; but it was noted that marked right ventricular hypertrophy was present in all twelve. A large " a " wave (Abrahams and Wood, 1951) was present in the right auricular pressure tracing in every case. Effort intolerance was present in all, but cardiac failure was not found.

The auricular sound could not be heard in any of over 100 healthy subjects, and it was concluded that it is not audible in the absence of cardiovascular disease.

DISCUSSION

The time relation of the auricular sound to electrical and mechanical events in the cardiac cycle suggests that it is produced in the ventricle by blood entering from auricular systole. Its configuration on the phonocardiogram resembles that of the third heart sound, which is also a filling sound produced in the ventricle. Unlike the third heart sound, however, the entry of blood from auricular systole does not give rise to audible vibrations in the normal ventricle: in every case with an auricular sound there was ventricular hypertrophy or ventricular ischæmia. It may be that hypertrophied or infarcted ventricular muscle is less tolerant of distension. This theory was originally propounded by Potain in 1885, when he wrote " The gallop . . . is more pronounced if the heart is not distensible: the failure of distensibility may depend either on a sclerotic thickening . . . or to a decrease in muscular tonicity." Duchosal (1935) similarly attributed the sound to the

" shock of ventricular incompressibility " when the left ventricle was diseased. Increased force of auricular contraction may also play a part, since a large " a " wave was seen in the right auricular pressure tracings in all 12 cases catheterized. Under these circumstances, filling gives rise to vibrations whose amplitude may approach that of the first heart sound (Fig. 4 and 5).

Audibility is further enhanced when, as the result of a P–R interval of 0·15–0·18 sec., the first heart sound is soft and the auricular and first sounds are widely separated. In one patient, the

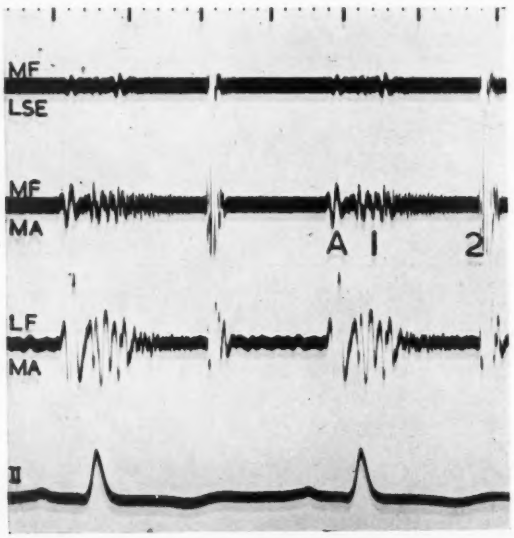

FIG. 4.—Large auricular sound in a patient with hypertensive heart disease.

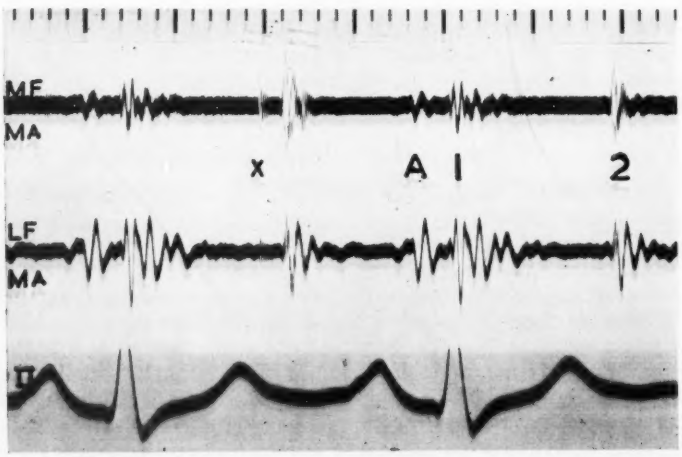

FIG. 5.—Large auricular sound in a patient, following cardiac infarction (X=artefact).

first component of a split first heart sound, although close to the auricular sound, was so small as to be inaudible at the apex: the auricular sound was therefore easily separated by the ear from the later component of the first sound (Fig. 6).

Clinical Significance. The particular association of the auricular sound with hypertension was first noted by Potain in 1875. Subsequently many observers have regarded the sign as having a bad prognostic significance and have stressed a relationship with cardiac failure (Lewis and Dock, 1934; Bramwell, 1935; Duchosal, 1935; Evans, 1943; and Levine and Harvey, 1949). In Miles's (1951) series, failure was not always present, but effort intolerance was invariably found.

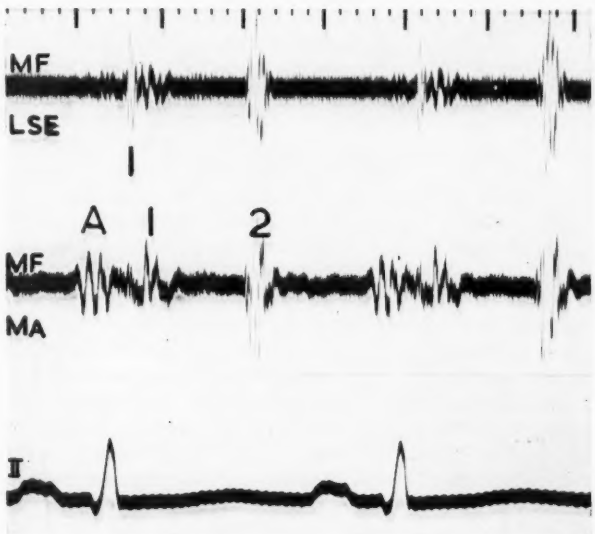

FIG. 6.—Auricular sound together with split first sound. At the apex (MA) the auricular sound and the second component only of the first sound were audible.

In the present series only 23 per cent of hypertensive patients with an auricular sound showed evidence of failure. The great majority were ambulant and able to follow their ordinary occupations. Death occurred in only 2 of 24 patients observed over periods of from three months to six years after the sound was first noted; and in four others in whom failure occurred, response to treatment was satisfactory. In five patients (including three with malignant hypertension who responded to medical treatment) effort tolerance has remained normal for 2 to 6 years. The auricular sound in hypertension indicates left ventricular hypertrophy rather than cardiac insufficiency; but either may occur without this sign being present (Table III).

Following myocardial infarction, the long-term prognosis was worse in patients in whom the auricular sound persisted after the acute attack. In 56 per cent there was cardiac failure or effort dyspnœa compared with an incidence of 22 per cent in those without the added sound. The lower incidence of angina in the patients with an auricular sound, shown in Table IV, is misleading, since so many were too dyspnœic to undertake much effort. Correlation with left ventricular enlargement was again high (80%), but the left ventricle was of normal size in 20 per cent. It should be noted that the sound may persist for months or years after the acute episode even in symptom-free patients.

The incidence in aortic valve disease was low. This was surprising in view of the considerable degree of left ventricular hypertrophy that was usually seen on the electrocardiogram. In cases

of aortic incompetence, it may be that the reflux from the aorta during diastole results in a pressure gradient which is unfavourable to atrioventricular bloodflow at the time of auricular systole. The rarity of the sound in aortic stenosis is more puzzling.

The incidence of failure among the 100 patients with an auricular sound was not high (21%). In fact, the auricular sound was essentially a sign of ventricular hypertrophy (or ischæmia). The usual cause of triple rhythm in heart failure is an abnormal third sound, which may appear to be mid-diastolic because of tachycardia. The latter may result in summation of the third sound with auricular vibrations thus giving rise to the loud triple rhythm commonly heard in heart failure.

Summary and Conclusions

One hundred patients with an audible auricular sound were studied in order to determine the mechanism and significance of this finding. The series comprised 46 cases with hypertension, 29 with myocardial infarction, and 25 with other conditions. Phonocardiograms were recorded in 74: in the 12 congenital cases they were taken synchronously with intracardiac pressure pulses. The clinical findings in these patients were compared with those in 205 patients with similar diseases, in whom the auricular sound was not detected, and in over 100 healthy subjects.

The sound occurs 0·12–0·17 sec. after the onset of the P wave and 0·05–0·09 sec. after the onset of auricular systole. These findings suggest that it is a filling sound produced in the ventricle by blood entering during auricular systole. The vibrations caused by this are normally inaudible, but are accentuated when the ventricle is hypertrophied or has undergone infarction.

The auricular sound was not heard in healthy subjects, nor in any case of heart disease in which both electrocardiogram and X-ray were normal.

In hypertension the sound was always associated with hypertrophy of the left ventricle. Although the patients with the added sound showed a higher incidence of cardiac failure three-quarters (77%) were free of heart failure and about one-quarter (25%) were free of all symptoms.

In cardiac infarction persistence of the sound was associated with left ventricular enlargement in 80 per cent of cases, and with cardiac failure or effort dyspnœa in 56 per cent, but 16 per cent remained symptom-free. The sound was seldom heard in aortic valve disease.

It is concluded that the auricular sound is a filling sound produced in the ventricle. It always indicates abnormality of the ventricle and is not audible in health, but is not direct evidence of cardiac failure.

I would like to express my thanks to Dr. Aubrey Leatham for the great interest he has shown in this study, and for advice and assistance in the preparation of this paper given by him and also by Sir John Patkinson, Dr. Paul Wood, Dr. William Evans, and Dr. Maurice Sokolow. My gratitude is due also to the other Physicians at the National Heart Hospital for permission to study the patients under their care: and to the technical staff of the Institute of Cardiology for their share in the recordings.

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UNILATERAL MEMBRANOUS PULMONARY VENOUS OCCLUSION, PULMONARY HYPERTENSION, AND PATENT DUCTUS ARTERIOSUS

BY

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A few patients with patent ductus arteriosus develop cyanosis from intermittent or established shunt-reversal caused by pulmonary hypertension. In these patients the Gibson murmur is absent and clinical and electrocardiographic evidence of right ventricular hypertrophy is found (Cosh, 1953; Hultgren *et al.*, 1953). The pulmonary hypertension can be the result of raised pulmonary vascular resistance, due to persistence of the fœtal pattern of pulmonary arteries and arterioles, to reflex pulmonary vaso-constriction, or to the development of degenerative changes in the pulmonary arterial tree. Increased resistance to blood flow beyond the pulmonary capillaries has not so far been suggested as a possible cause of pulmonary hypertension in patients with patent ductus. The case reported here had a membranous occlusion of the right pulmonary veins, as well as pulmonary arterial hypertension, a patent ductus arteriosus, and central cyanosis. The unilateral pulmonary venous occlusion was responsible for a bizarre and puzzling X-ray picture of the chest. The relationship between the pulmonary venous occlusion, the pulmonary arterial hypertension, and the failure of the ductus arteriosus to close is worthy of consideration.

Case Report

In June, 1950, a girl, aged 10 years, was referred to one of us (I.G.W.H.) from abroad as a case of cyanotic congenital heart disease. Her parents were healthy and unrelated. Her mother had malaria early in pregnancy. Labour was uneventful. She had one younger brother, aged 7 years, who was healthy.

History. A full-time baby weighing 8 lb. she was breast-fed with supplementary feeds for three months, but was difficult to rear and was regarded as a "poor, sickly, little thing." At one year she weighed 16 lb., had cut one tooth, and was beginning to toddle. Cyanosis, noted intermittently after the age of two months, was hardly apparent in the second year, but thereafter was nearly always evident and was much worse after exercise. She was never able to play games and would squat after running only about 20 yards, but she learned to ride on horseback. She led a sheltered life at home, taught by her mother, a retired schoolteacher. Her mental development was normal. Her disability did not alter appreciably between the ages of 2 and 10 years, but at the age of 6 to 7 years, she had, in the space of 18 months, three attacks of "pneumonia," in each of which her life hung in the balance.

Examination (June, 1950). She was a slender, high-spirited child, 55 in. tall, and weighing 61 lb. Cyanosis of the lips was conspicuous when she had finished undressing but diminished after she had rested on the couch. Clubbing was possibly more marked in fingers than in toes. There was marked sinus arrhythmia. The heart was not enlarged clinically and there was no thrill. There was a loud, widespread systolic murmur, maximal in the pulmonary area, but no diastolic murmur. The femoral pulses were easily palpable.

The blood pressure in the arms was 110/80 mm. Hg. Small hæmangiomata on the nape of the neck were the only other abnormality. The hæmoglobin was 15·6 g./100 ml., the red blood cells 5·3 million per c.mm., and the packed cell volume 48 per cent. The brachial arterial oxygen saturation was 82·5 per cent.

The electrocardiogram showed normal rhythm and marked right ventricular hypertrophy.

Chest X-rays, dating back to 1944 (age 4 years), showed slight generalized cardiac enlargement, a small aortic knob, and prominence of the pulmonary artery segment. The left lung field was normal, but the right showed increased vascularity of unusual pattern (Fig. 1). Bronchoscopy and bronchography showed a normal bronchial tree in each lung.

Subsequent History. She remained well until April, 1953, when she developed a febrile illness diagnosed as " influenza." From that time she became increasingly breathless on exertion and the cyanosis deepened and was less variable. Eventually she was able to walk only 10 to 20 yards. In view of this rapid deterioration she was referred for further investigation.

Examination (November, 1953). Now aged nearly 14 years, she was well-nourished and showed the normal changes of puberty. She was deeply and equally cyanosed in face and extremities. Fingers and toes were equally and grossly clubbed. Apart from constant fine râles at the right lung base, the physical signs were unchanged. The hæmoglobin was 17·1 g./100 ml., the red blood cells 7·6 million per c.mm., and the packed cell volume 66·5 per cent.

The electrocardiogram showed gross right ventricular hypertrophy. Chest X-ray showed more marked changes in the right lung (Fig. 2).

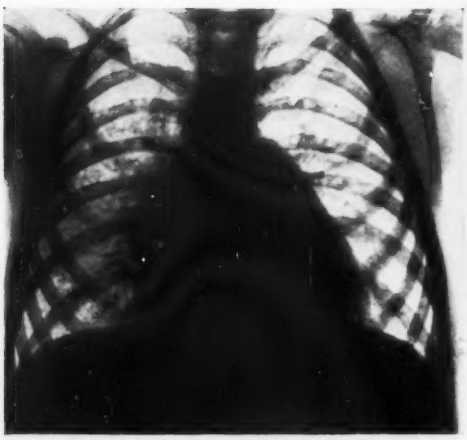

FIG. 1.—Chest X-ray at age of 4 years, showing increased vascular markings in right lung.

FIG. 2.—Chest X-ray at age of 13 years, showing more marked changes in the right lung.

Cardiac Catheterization. The catheter was passed via the right side of the heart into several branches of both right and left pulmonary arteries, and through a patent ductus arteriosus into the descending aorta. The pulmonary arterial and aortic pressures were not measured simultaneously but were of the same order, the mean pressure in the pulmonary arteries being higher than that in the aorta (Fig. 3). The data from catheterization sufficed to make a diagnosis of patent ductus arteriosus with gross pulmonary hypertension; there was suggestive evidence of right-to-left shunt through the ductus. A pulmonary arterial wedge pressure was recorded on the left side but the record was spoilt by artefact. This was not repeated and arterial punctures were not made.

Operation was again considered inadvisable and angiocardiography was therefore not done. The mother was told that the outlook was poor. The girl was allowed home, but became seriously ill with a syncopal attack and intense cyanosis a month later and was re-admitted to hospital next day with fever to 104° F., pulse rate of 130 a minute, and respiratory rate of 50 a minute. Despite intensive antibiotic therapy and nursing in an oxygen tent, she died on the second day.

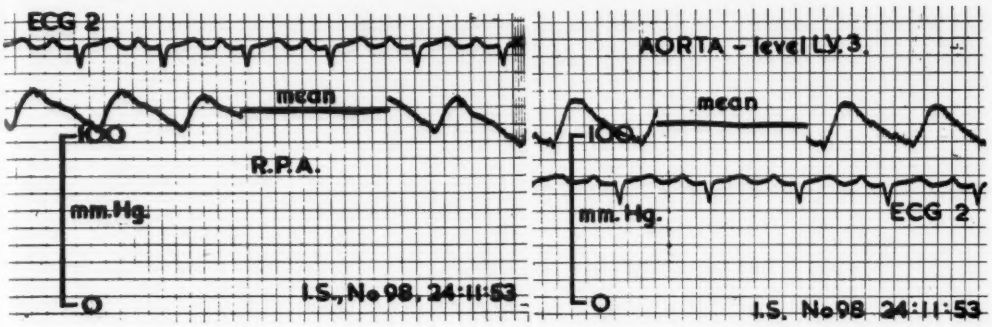

FIG. 3.—Pressure tracings obtained from right main branch of pulmonary artery and abdominal aorta.

DATA FROM CARDIAC CATHETERIZATION

	Pressure mm. Hg (Capacitance manometer)		Oxygen saturation percentage (Haldane)
	Systolic/ diastolic	Mean	
Abdominal aorta	123/96	111	57
Left pulmonary artery	130/104	119	37
Right pulmonary artery ..	133/100	118	—
Right ventricle	131/12	61	32
Right atrium	—	11	—

POST-MORTEM FINDINGS (*Dr. T. Bird*)

Patent ductus arteriosus, congenital diaphragm obliterating orifice of right pulmonary vein, gross venous congestion and hæmosiderosis of right lung, and endocarditis of tricuspid valve.

Cardiovascular System. The heart was enlarged (320 g.) and globular, the anterior aspect being mainly right atrium and right ventricle (Fig. 4). The right atrium was dilated, with thickened wall, and normal caval entrances. The tricuspid valve showed many opaque white vegetations, up to 4 mm. in diameter, some with a small pedicle, all firmly adherent; otherwise the cusps, chordæ, and papillary muscles were normal. The right ventricle was dilated; the myocardium was thickened, with tiny scattered areas of fibrosis in the posterior wall. The pulmonary artery, arising normally, was dilated (22 mm. diameter). The ductus arteriosus (10 mm. long and 5 mm. diameter) arose from the origin of the left pulmonary artery; there was slight intimal thickening in the left pulmonary artery opposite the ductus, but not in the aorta. The inter-atrial septum showed no communication. The left atrium was of normal size and thickness. The left pulmonary veins entered normally, with a short common trunk. The right pulmonary veins were of normal diameter, but were felt as hard cords, and appeared to unite just before reaching the atrium. The opening into the atrium of the right upper pulmonary vein was obstructed by a membranous diaphragm containing two tiny openings, situated centrally and inferiorly, and each admitting only a very fine probe (Fig. 5). The lower pulmonary vein ended blindly close by, and did not communicate either with the upper vein or the atrium. The veins contained unorganized clotted blood forming a cast; this extended into the small branches in the lung. The main veins were not dilated, but their walls were two to three times thicker than those of the corresponding veins on the left side. The mitral valve was normal. The left ventricle was dilated and the wall was 10 mm. thick at the base, small patches of fibrosis

FIG. 4.—Anterior aspect of heart, showing the large right ventricle and ductus arteriosus.

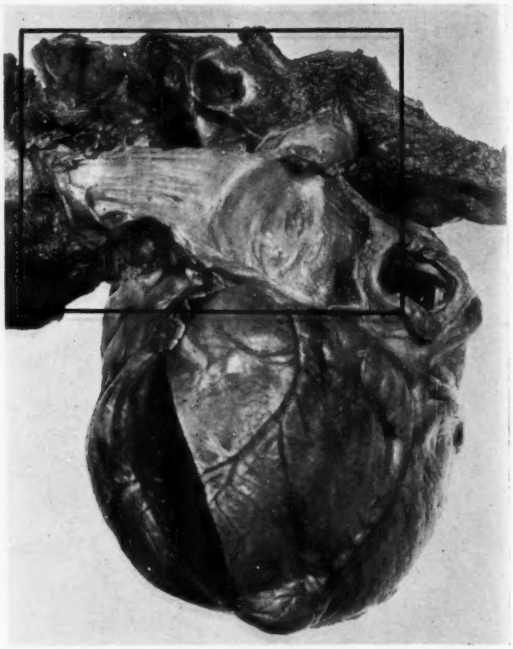

FIG. 5.—View of heart from behind. The posterior wall of the left atrium has been removed.

FIG. 6.—Diagram illustrating the anatomy of the area within the rectangle in Fig. 5.
(A) Common trunk of left pulmonary veins laid open.
(B) Central punctum of membrane occluding orifice of upper right pulmonary vein.
(C) Interior of left atrium.

being seen in the anterior wall near the septum. The coronary arteries were normal. The aorta (10 mm. in diameter at origin), showed a few small intimal fatty plaques in the ascending part.

Respiratory System. The pleural cavities each contained 150 ml. of clear yellow fluid; there were no adhesions. The lungs filled the chest and met anteriorly to cover the pericardium. There were striking differences between the two lungs. The left lung showed a normal pleural surface; on section it was dull, dark red with congestion and was moderately œdematous, especially in the lower lobe. The pulmonary artery branches were distinctly atheromatous, the veins normal. There was no evidence of consolidation or infarction, and no visible hæmosiderosis. The right lung was more voluminous. The subpleural venous system, particularly of the lower lobe, was grossly dilated, engorged, and tortuous (Fig. 7). This prominent network of vessels converged posteriorly to form a large leash of veins which passed in the posterior pleural fold to empty into the right azygos venous system. No comparable veins were seen on the left side. Scattered brownish-black spots of hæmosiderosis were visible in the pleura between the distended veins.

FIG. 7.—Anterior aspect of right lung, showing hæmosiderosis throughout and pleural venous network most marked in lower lobe.

On section, the right lower lobe was firm, slightly œdematous, and showed obvious foci of hæmosiderosis. The right upper and middle lobes were paler and drier, but of similar consistency; the foci of hæmosiderosis were not so obvious on section as on the pleural surface. No evidence of consolidation or infarction was seen anywhere. All the cut surfaces showed prominent dilated veins, filled with a cast of dark red, clotted blood, without evidence of organization. The pulmonary artery branches were also prominent; all showed atheroma with many raised yellow plaques, but neither calcification nor thrombosis. The bronchi were congested and contained mucopus.

Other organs. The abdominal cavity contained approximately 250 ml. of clear yellow fluid. The liver, spleen, and kidneys showed venous congestion. Apart from a thin-walled, simple cyst, 4 cm. in diameter, in the right ovary, the remaining viscera were normal.

Discussion

Although the diagnosis of patent ductus arteriosus with pulmonary arterial hypertension was made in life, the inequality of the vascular patterns of the lungs was not explained until the venous engorgement and hæmosiderosis of the right lung were revealed post mortem. The pulmonary venous occlusion might have been recognized in life had angiocardiography been justified, and might have been suspected at catheterization if pulmonary arterial wedge pressures had been recorded in both lungs and found to be higher on the right side. This would have indicated right pulmonary venous hypertension since wedge pressures are said to distinguish pulmonary arterial hypertension due to arteriolar resistance from that due to resistance beyond the capillaries (Swan *et al.*, 1954).

Our interpretation of the findings in this case is that the primary abnormality was the membrane that almost completely occluded the right pulmonary veins. This presumably led to right pulmonary venous hypertension and, reflexly, to generalized pulmonary arterial hypertension. As the patient was cyanosed from early infancy we think that a right-to-left shunt through the ductus was present from birth. The pulmonary hypertension may possibly have prevented the ductus from closing. Inadequate oxygen saturation of blood flowing through the left lung may have contributed to the central cyanosis. Blood flowing through the right lung was largely returned to the systemic circuit. The tricuspid endocarditis was thought to be a terminal event; it was certainly of recent origin and had produced no obvious infarctions in either lung. A detailed study of the histology in this case, particularly in relation to the unequally distributed hæmosiderosis, is being made.

Summary

A 13-year-old girl, handicapped from infancy by breathlessness on exertion, showed cyanosis from the age of two months, a tendency to squat, and, later, obvious digital clubbing. Unequal radiological opacity of the lung fields was present from at least the age of 4 years, the left lung appearing normal and the right lung unduly vascular. Cardiac catheterization demonstrated a patent ductus arteriosus and pulmonary hypertension and suggested right-to-left shunt through the ductus.

Necropsy revealed a congenital membranous occlusion of the right pulmonary veins, hæmosiderosis of the right lung, gross distension of the pleural venous plexus with drainage of the right lung to the systemic veins, right ventricular hypertrophy, and patent ductus arteriosus.

It is suggested that the congenital diaphragm obstructing the venous return from the right lung led to pulmonary arterial hypertension and prevented the ductus arteriosus from closing.

Our thanks are due to Professor A. C. Lendrum of the Department of Pathology, St. Andrews University, for his co-operation, and to Dr. T. Bird for the post-mortem report.

Fig. 2 is from a skiagram sent by Dr. J. G. G. Mitchell. The photographs are by Mr. F. Duncan.

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PATENT DUCTUS ARTERIOSUS WITH PULMONARY HYPERTENSION

BY

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For many years there have been occasional reports of patients with persistent patent ductus arteriosus who have not had the usual Gibson murmur and who at necropsy have been found to have thickening of the small pulmonary arteries and right ventricular hypertrophy (Holman, 1925; Apert and Baillet, 1932; Keys and Shapiro, 1943; Chapman and Robbins, 1944; Douglas *et al.*, 1947; Ulrich, 1947). With the aid of cardiac catheterization, it is now possible to diagnose such atypical cases during life, and during recent years many of these patients have been described (Dushane and Montgomery, 1948; Bouchard *et al.*, 1950; Johnson *et al.*, 1950; Mannheimer, 1950; Novelo *et al.*, 1950; Pritchard *et al.*, 1950; Campbell and Hudson, 1951; Myers *et al.*, 1951; Adams *et al.*, 1952; Cosh, 1953; Dammann *et al.*, 1953; Hultgren *et al.*, 1953). The feature common to all these patients is the presence of a raised pressure in the pulmonary artery giving rise to right ventricular hypertrophy. The pressure in the pulmonary artery may in fact exceed that in the aorta, in which case there is a reversal of flow along the ductus with consequent cyanosis.

The following is an account of a patient with patent ductus arteriosus and pulmonary hypertension in whom the information as to natural history, physiology and morbid anatomy seems to be unusually complete.

Case Report

The patient, a housewife of 43, was first seen in December, 1952. Since the preceding summer she had had four attacks of rapid, irregular beating of the heart each lasting several hours, and there had been increasing shortness of breath on exertion. The heart had been found to be abnormal at the age of eight, but there had been no disability before her forty-third year. She had had normal pregnancies and deliveries at 25 and 29 years of age.

There was no cyanosis or clubbing and no evidence of heart failure. The pulse was regular and of a collapsing nature with excessive pulsation visible in the carotids. The apex beat was in the anterior axillary line in the sixth intercostal space and the thrust of a hypertrophied right ventricle could be felt just to the left of the sternum. There was a remarkably strong diastolic thrill in the second and third spaces to the left of the sternum. This was associated with an intense diastolic murmur loudest in this area, but audible over the entire prækardium. It occupied the whole of diastole and was of a very coarse character, seeming to the ear to include vibrations of a lower pitch than are heard in the usual murmur of regurgitation from pulmonary artery or aorta. The timing of the murmur was confirmed later by phonocardiography (Fig. 1). There was no murmur in sytole.

Skiagrams and cardioscopy showed some enlargement of each ventricle and considerable dilatation of the trunk of the pulmonary artery and of its two main branches; in these an excessive intrinsic pulsation was visible (Fig. 2). The aorta also was thought to be a little large. A cardiogram was interpreted as showing evidence of hypertrophy of both ventricles.

Two weeks later she was admitted urgently to hospital with congestive heart failure and auricular fibrillation. The venous pressure was 26 cm. water, rising to 30 cm. on pressing over the liver. She was

* Wiltshire Memorial Research Scholar.

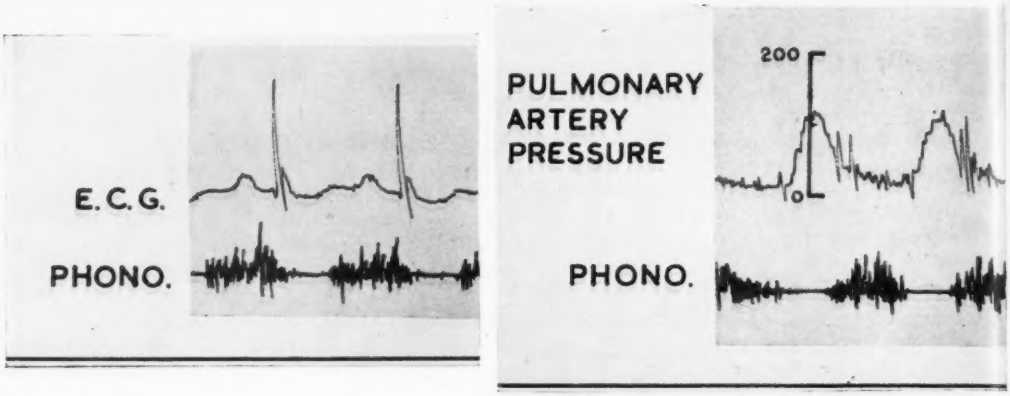


FIG. 1.—Phonocardiogram, with simultaneous electrocardiogram and pulmonary artery pressure tracing, to show the diastolic timing of the murmur.

FIG. 2.—Postero-anterior view of the heart.

treated with rest, digitalis, a diet poor in salt, and injections of mersalyl. Within six weeks she was well again and the heart in normal rhythm.

Cardiac catheterization was carried out at that time. The oxygen content of the blood in the pulmonary artery (88%) was found to be very much higher than that in the right ventricle (73%), signifying a shunt from the aorta into the pulmonary artery. In addition, the sample from the inflow tract of the right ventricle was more highly oxygenated than that from the atrium (66%). This difference of

1·3 vols. per cent is probably significant (Holling and Zak, 1950) and was thought to indicate pulmonary incompetence.

The pressure recordings showed a high "*a*" wave in the right atrium. The systolic pressure in the pulmonary artery (140/10) was much higher than normal, but the diastolic pressure was within the normal range. The pulse pressure was therefore wide and this would bear out the presence of severe pulmonary incompetence. The mean pulmonary artery pressure was high (55mm.).

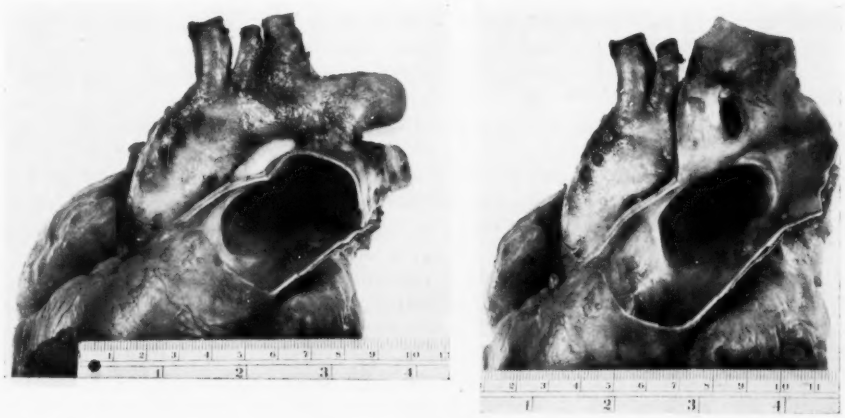
The systolic pressure in the pulmonary artery (140/10) was found to equal the systolic pressure in the femoral artery (140/20). Although these records were not simultaneous and although the curve of pressure in the femoral artery may not correspond exactly with that in the aorta (Hamilton and Dow, 1939) it was thought that the similarity of these two pressures might help to explain the physical signs, for no murmur could be heard in systole and it seemed reasonable to conclude that the gradient of pressure between aorta and pulmonary artery was insufficient to cause a flow along the ductus during this part of the cycle. The similarity in oxygen content of samples of blood taken from the right brachial (96%) and left femoral arteries (97%) ruled out the presence of a significant right-to-left shunt through the ductus.

An angiocardiogram showed the very great dilatation of the pulmonary artery trunk and its main divisions, while the peripheral branches appeared normal. There was no visible flow of dye from pulmonary artery to aorta.

Shortly after these investigations had been carried out, it was learned that she had been a patient at the Hospital for Sick Children at the age of nine and in the Middlesex Hospital during her first pregnancy when she was 25. These hospitals have kindly sent details of their findings. At the age of nine she was noted to have a systolic murmur in the pulmonary area and a loud pulmonary second sound. At the age of 25, when she was under Dr. G. E. S. Ward's care, the findings in the pulmonary area were noted as follows: "Thrill palpable throughout systole and diastole but mainly in diastole. Murmur of harsh character heard throughout systole and diastole. First sound audible. Second sound absent. Pulmonary pulsation palpable."

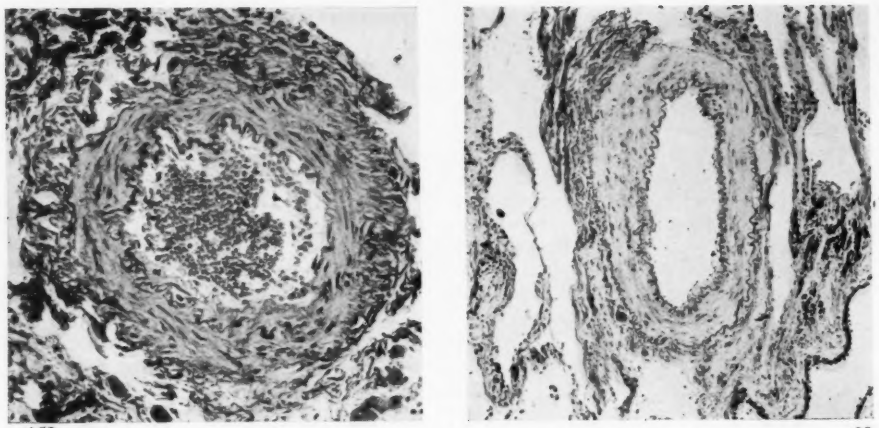
The diagnosis of a patent ductus arteriosus seemed therefore assured and an operation was advised, but the patient was unwilling to undergo this. She was allowed home at the end of February, 1953, but failure recurred, necessitating re-admission to hospital in June and again in August. At this time auricular fibrillation returned and the tricuspid valve became incompetent as judged by a sustained systolic venous pulse wave visible in the neck and palpable in the distended liver. She died in September of the same year, a little over a year after the onset of symptoms.

Necropsy showed a patent ductus arteriosus arising just beyond the origin of the left pulmonary artery (Fig. 3A). At this point the aorta abutted on the pulmonary artery and there was virtually no length to



A B

FIG. 3.—Frontal view of heart. (A) The anterior wall of the pulmonary artery has been partly cut away; the external appearance of the ductus is shown. (B) The anterior wall of the pulmonary artery has been reflected to show the internal appearance of the ductus.



×150 ×80

FIG. 4.—Sections of small pulmonary arteries.

the ductus. The pulmonary artery and two main branches were greatly dilated, the circumference of the main trunk being 12 cm. The aorta was also dilated, with a circumference of 9 cm. The internal diameter of the ductus was a little less than 1 cm. (Fig. 3B). There was no " impingement plaque " in either vessel. Both ventricles were hypertrophied, the thickness of the right ventricular wall varying between 1 and 1·5 cm., and that of the left ventricular wall between 1·5 and 2 cm. The pulmonary valves were a little thickened and water flowed readily through them from the pulmonary artery into the right ventricle.

The lungs were dry, and the small pulmonary arteries appeared thickened and prominent on the cut surface. Under the microscope (Fig. 4) there was widespread thickening of the walls of the small muscular branches of the pulmonary artery. This could be seen to be due to a pronounced hypertrophy of the muscle of the media of these vessels. The adventitia showed an excess of fibrous tissue. There was also some proliferation of the intima of varying degrees in arterial branches of all sizes, but this was not outside the normal limits for the age.

DISCUSSION

Why pulmonary hypertension is present in some patients who have a patent ductus arteriosus and not in the majority is not yet known. In some instances it has been thought to be due to a congenital abnormality of the small pulmonary arteries. In the fœtus, these vessels have a muscular media (Civin and Edwards, 1951) which is associated with a high resistance (Hamilton *et al.*, 1937) and an abnormal persistance of this state of affairs might be the basis of pulmonary hypertension after birth (Civin and Edwards, 1950; Novelo *et al.*, 1950; Campbell and Hudson, 1951; Cosh, 1953; Hultgren *et al.*, 1953). To support this view is the fact that many of the patients reported are children; and, judging by the presence of cyanosis, a pressure in the pulmonary artery high enough to reverse the shunt often occurs early in life in these patients and may even be present at birth.

It is also possible that the high pressure in the pulmonary artery is acquired after birth. In only one previous instance, however, has a Gibson murmur been noted which subsequently disappeared, presumably with the onset of pulmonary hypertension. This is the patient reported by Campbell and Hudson (1952) who were of the opinion that the pulmonary hypertension was of acquired origin. In the patient described here, the high pressure in the pulmonary artery seems also to have developed later in life. For she is known to have had a Gibson murmur at 25 which was replaced by a purely diastolic murmur by the age of 43.

If it be granted that the natural history of this patient's disease speaks against a congenital cause for the high pressure in her pulmonary artery, then it is hard to avoid the conclusion that a persistently increased flow of blood played some part in the initiation of this hypertension later in life.

In considering how this might have come to pass, there are several diverse facts that have to be reconciled.

In the first place, exercise may cause a considerable increase in flow of blood through the lungs of a normal person with little or no rise in pressure (Hickam and Cargill, 1948; Riley *et al.*, 1948; Cournand *et al.*, 1950; Dexter *et al.*, 1951). The pressure in the pulmonary artery is also usually normal in those abnormalities, such as patent ductus arteriosus or atrial or ventricular septal defects, which cause a persistently increased pulmonary blood flow. Yet it is in just these abnormalities that severe pulmonary hypertension is liable to occur. When this happens, the pulmonary " arteriolar " resistance is found to be higher than normal and it is this increased resistance and not any increase in flow which plays the important part in causing the pulmonary hypertension. Indeed, the rise in pressure in the pulmonary artery tends of itself to inhibit or even reverse the shunt of blood so that the flow through the lungs may actually be less than the systemic flow. In such patients the cyanosis may be observed to increase gradually in intensity. So that, beyond a certain stage, the pulmonary vascular resistance continues to rise despite the fact that the pulmonary blood flow is thereby progressively reduced below the systemic flow.

The estimation of pulmonary blood flow in this patient must be less accurate than usual owing to the presence of two distinct streams of blood in the pulmonary artery (Eppinger *et al.*, 1941). The addition of severe pulmonary incompetence, however, may well offset this to a large extent by increasing the efficiency of mixing of these streams, and this is borne out by the similarity in oxygen content of the two samples taken from the pulmonary artery. Thus the indications are that the flow through the lungs was between three and four times that through the systemic circulation and that the pulmonary " arteriolar " resistance was also somewhat raised.

This increase in pulmonary " arteriolar " resistance can be correlated with the hypertrophy of muscle and the fibrosis found in the walls of the small pulmonary arteries. The same histological appearances have been described in similar patients by several authors, whatever view has been taken of the origin of the pulmonary hypertension (Douglas *et al.*, 1947; Edwards *et al.*, 1949; Swan *et al.*, 1949; Johnson *et al.*, 1950; Campbell and Hudson, 1951, 1952; Dammann *et al.*, 1953; Cosh, 1953; Hultgren *et al.*, 1953). In this patient, the preponderance of muscle over fibrous tissue in the walls of the small pulmonary arteries was confirmed pharmacologically during life by the action of acetylcholine. When this was injected through the catheter, it caused a great fall in pressure in the pulmonary artery which has not been observed in patients in whom this pressure is normal but which occurs in varying degree in the presence of pulmonary hypertension (Harris, 1953). Similar pharmacological studies have been reported by Halmgáyi *et al.* (1953).

The small pulmonary arteries of the normal lung are only meagerly provided with muscle (Brenner, 1935*a*; Parker and Weiss, 1936; Henry, 1952) and this is also usually the case in patients with patent ductus arteriosus (Welch and Kinney, 1948). Hypertrophy of the medial muscle in patent ductus seems in fact to be related to the presence of a high pressure in the pulmonary artery and not directly to increased flow. An excess of muscle tissue is universally the expression of an increased muscular work. Hypertrophy of the muscle of the media of a vessel must therefore imply active vasoconstriction occurring intermittently or continuously for a prolonged time. The effect of acetylcholine verifies the presence of such vasoconstriction in the pulmonary vessels of this patient.

Hypertrophy of the muscle of the media is not therefore the cause of arterial constriction but its effect. There is much muscle in the media of the small pulmonary arteries of the fœtus. This is also found in the same arteries of patients with a patent ductus arteriosus and pulmonary hypertension. It cannot, however, be argued that a simple persistence of this muscle after birth would cause a high pressure in the pulmonary artery. What has to be postulated is a persistence of active vasoconstriction in these vessels which will maintain the bulk of the muscle. For it seems the universal rule that muscle tissue will atrophy when it ceases to be used.

In patients with mitral stenosis there is also a hypertrophy of the medial muscle in the small pulmonary arteries (Parker and Weiss, 1936; Larrabee *et al.*, 1949; Henry, 1952) and this is accompanied by an increase in the resistance to flow specifically at the level of these vessels. Yet at no

time in the evolution of this disease is there any abnormal increase in flow of blood through the lungs, but simply a generalized increase in intravascular pressure throughout them. The increase in pulmonary " arteriolar " resistance is diminished following valvotomy when the pressure falls throughout the lesser circulation (Draper *et al.*, 1951; Carlotti *et al.*, 1952; Lukas and Dotter, 1952). In mitral stenosis, therefore, the small pulmonary arteries appear to constrict and become muscular in response to a prolonged increase of pressure in the lesser circulation. On the other hand, a similar response has not been noted in normal people when the pressure has been artificially raised for a short period by infusing large volumes of fluid intravenously (Doyle *et al.*, 1951; Witham *et al.*, 1951). In the normal person, however, the medial muscle of these vessels is perhaps too scanty to be expected to cause any effective vasoconstriction in response to this particular stimulus, whereas a frequent repetition or continuation of the stimulus over a prolonged period might well cause the muscle to increase in bulk and thus in power.

The effects of exercise in patients with mitral stenosis suggest that this may be so, for Hickam and Cargill (1948) and Bayliss *et al.* (1950) found that occasionally there occurred a rise of pressure in the pulmonary artery far greater than could be explained by a fixed obstruction at the mitral valve. This is, however, by no means always the case (Draper *et al.*, 1951; Gorlin *et al.*, 1952; Lukas and Dotter, 1952).

How a rise in pressure in the pulmonary artery could provoke a constriction of its small branches is a matter for conjecture. The mechanism may be a nervous one, for afferent impulses have been demonstrated in the vagus which appear to arise from the pulmonary arterial tree and which are stimulated by each pulse wave (Walsh and Whitteridge, 1945; Whitteridge, 1948; Pearce and Whitteridge, 1951).

During cardiac catheterization in patients with many different types of lesion, the pulmonary artery pressure is often seen to vary considerably from moment to moment. This is particularly so when the patient is nervous and apprehensive. It might be expected that such fluctuations in the pulmonary artery pressure would more often bring it above the normal range in a patient with an increased flow of blood through the lungs than in a normal person, despite the fact that under basal conditions the pressure in the pulmonary artery is usually normal in such patients. It may be that this was the way in which constriction was at first stimulated in the small pulmonary arteries of the patient described here.

With these considerations in mind, the following sequence of events is put forward as a possible explanation of the development of pulmonary hypertension in some patients with a persistent patent ductus.

The increase in flow of blood through the lungs may of itself be high enough to cause some slight rise in pressure in the pulmonary artery. Or, more likely, the abnormal rise in pressure at first occurs only intermittently. Such a rise in pressure in some unknown way causes the small pulmonary arteries to constrict. The response of these vessels is at first very weak, as their medial muscle is small in bulk. Frequently repeated or continued vasoconstriction, however, eventually causes this muscle to hypertrophy. This in turn increases the power of constriction so that what was originally possibly a " vestigial " function (Dixon and Hoyle, 1928) becomes a very important activity. As the vasoconstriction increases in power, so the pressure in the pulmonary artery is raised still further and thus a vicious circle of hypertension and vasoconstriction is initiated. This vicious circle will continue despite the fact that the flow of blood through the pulmonary artery is progressively reduced. A further result of hypertension is the development in the small pulmonary arteries of intimal fibrosis (Civin and Edwards, 1950; Edwards and Chamberlin, 1951) which will still further increase their resistance. The laying down of fibrous tissue in the walls of these arteries may eventually impair their flexibility so that variations in calibre become mechanically more and more limited and the activity of the medial muscle, therefore, less and less important. By this time the damage is presumably permanent.

It still remains to explain why this condition occurs predominantly in children and young adults and often appears to have its origin in infancy. Perhaps the clue to this lies in the histological structure of the small pulmonary arteries in the first few months of life. Civin and Edwards

(1951) have shown that the change from fœtal to post-natal structure in these vessels takes several months and during this time the media is excessively muscular. Hence at this time they are likely to be more responsive to the effects of high pressure in the manner outlined above, and the conditions are uniquely such as will foster the first stages of the vicious circle of hypertension and vasoconstriction.

There are several causes that might have initiated this vicious circle so much later in life in the patient described here. It is possible that the subintimal fibrosis which develops with advancing age and which is encouraged by an increased flow of blood (Welch and Kinney, 1948) may have had such an effect. The gradual development of a " window " type of ductus, as suggested by Dry *et al.* (1948), may have led to an increased shunt. Finally, the development of pulmonary incompetence by causing a high systolic pressure in the pulmonary artery may have evoked a repetitive constriction in the small branches.

Summary

A patient with patent ductus arteriosus is described in whom the combination of pulmonary hypertension and pulmonary incompetence seemed to allow shunting of blood only in diastole. Because of this, the Gibson murmur which had been observed 18 years previously had given place to a murmur confined to diastole. The mechanisms whereby such a rise in pressure in the pulmonary artery might have arisen are discussed and it is suggested that small and intermittent elevations of pressure in the pulmonary artery may have eventually initiated a vicious circle of vasoconstriction and hypertension.

I am very grateful to Dr. Terence East for allowing me to study his patient and publish these results, and for suggesting the main lines of thought in the discussion of this paper. I am also indebted to Professor H. A. Magnus for his criticism and for advice on the morbid anatomical details.

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LONG SURVIVAL WITH INFERIOR VENA CAVA DRAINING INTO LEFT ATRIUM

BY

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Developmental anomalies of the inferior vena cava are not infrequent. The majority cause no circulatory disturbance, but a small number result in veno-arterial communications that allow only a short period of postnatal life (Taussig, 1947).

Clinical and anatomical details are given below of an unusual case in which termination of the inferior vena cava in the left atrium was the only congenital abnormality affecting the circulation. Cyanosis was constantly present, there were few signs of heart disease and the patient lived actively for 32 years. The available details of her history, the physical signs, and the investigations performed are sufficient to assist in the recognition of future cases and are therefore described fully. We were unable to find previous records of a similar case or of an identical anatomical defect.

Case History

The patient was a married woman who died in 1953 at the age of 32. At the age of 4 years she had pneumonia and was subsequently noticed to be cyanosed. At 7 congenital heart disease was diagnosed. She had no symptoms apart from slight breathlessness on exertion, and was able to live a normal life and play games at school. From the age of 14 she worked as a domestic servant and college bedmaker until she married at 18. At 19 she became pregnant but the child died shortly after birth. Thereafter she had a succession of miscarriages at 4, 3, and 5 months respectively, and at the age of 23 was seen by one of us (L.C.) when she was again 24 weeks pregnant. At that time she suffered from considerable breathlessness on exertion and some swelling of the ankles but her condition was otherwise good. She was sturdy and well-proportioned and weighed 8 st. 12 lb. (56 kg.).

Examination showed severe cyanosis and clubbing of the fingers, but no other abnormalities. No murmurs were heard then or on any subsequent occasion and the heart sounds were normal. The blood pressure was 140/90, and the urine was normal. X-ray and screening showed no abnormality of the heart or lungs (Fig. 1). The cardiogram showed inversion of TII and deep inversion of TIII but was otherwise normal (Fig. 2). Blood count showed: red cells 6·9 million per cu. mm. and hæmoglobin 17 g. per 100 ml. Wasserman reaction negative. The pregnancy was allowed to continue and a normal full-term infant was born who still survives. She made a good recovery and appeared none the worse for her confinement.

A few weeks later she attended Ophthalmological Out-Patients with embolism of a branch of the right retinal artery, but did not again visit the Cardiac Clinic until the age of 28, when the clinical symptoms and signs were unchanged (red cells 6·4 million per cu. mm., and hæmoglobin 19·4 g. per 100 ml.; circulation time—arm-to-lung 17 sec., arm-to-tongue 24 sec.).

At 29 she again became pregnant, and was readmitted with toxæmia of pregnancy, blood pressure 180/120, and severe albuminuria. Her symptoms cleared up after a miscarriage, the fœtus weighing 2½ lb. (1·1 kg.), and the blood pressure fell to 130/70. Soon after this she developed tonsillitis followed by congestive heart failure and multiple pulmonary emboli. Pyrexia was prolonged and although blood cultures were sterile she was given 146 mega units of penicillin in six weeks. She again made a gradual recovery and was finally discharged eight months after her confinement and was soon well enough to do housework again.

Subsequent progress was uneventful and she continued to lead a comparatively active life until the age of 32 years. Then one day while stretching up to a high shelf she collapsed suddenly and died.

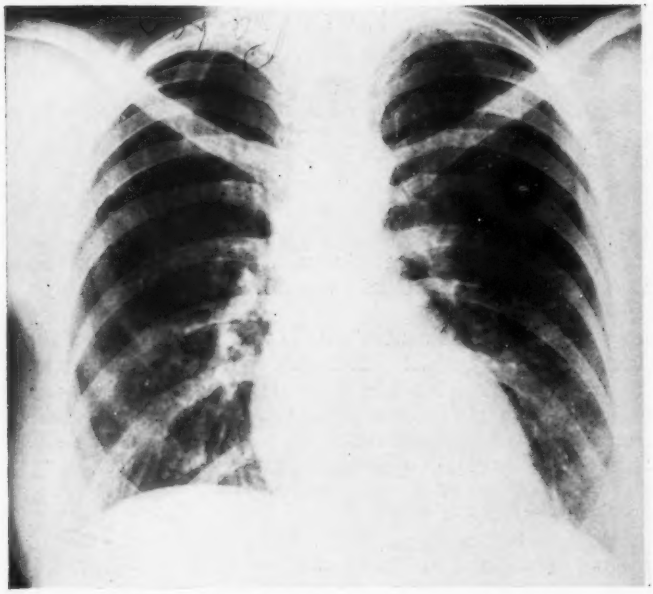

FIG. 1.—X-ray of chest at the age of 23 years.

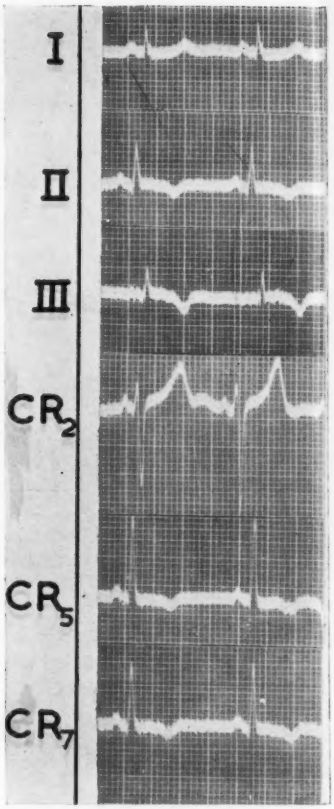

FIG. 2.—Electrocardiogram, showing inversion of TII and deep inversion of TIII at the age of 29 when the blood pressure was 180/120 from toxæmia of pregnancy. The limb leads were identical at 23 years of age.

NECROPSY REPORT

Necropsy was performed 24 hours after death. The body was that of a well-nourished young woman (weight 55·5 kg.), and showed generalized cyanosis which was most pronounced in the extremities. There was slight clubbing of all fingers and toes.

The heart occupied its normal position and weighed 450 g. The inferior vena cava passed proximally from the upper surface of the diaphragm and entered the left atrium. At its termination this vessel measured up to 3·5 cm. in diameter and up to 0·5 cm. in thickness (Fig. 3). (All measurements were confirmed on the preserved specimen.) The anatomical relationships of the veins below the diaphragm were normal, the inferior vena cava lying to the right of the anterior surface of the vertebral column and being formed by the union of two common iliac veins. The hepatic veins were considerably dilated. The superior vena cava 1·5 cm. in diameter, was joined by a greatly dilated azygos vein and entered the right atrium. Fibrous tissue obliterated the left internal jugular and the left innominate veins. The subclavian veins were not examined.

FIG. 3.—Dorsal view of the heart, showing the left inferior vena cava.

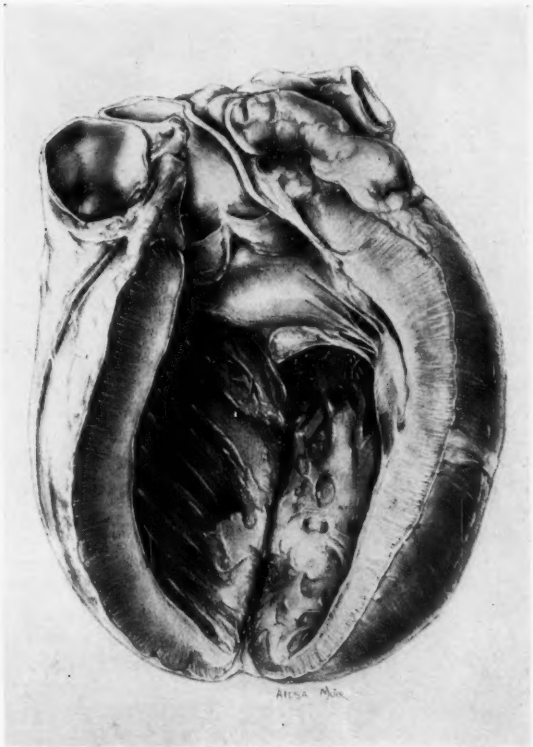

FIG. 4.—The opened left ventricle with the old infarct.

The coronary sinus (diameter 0·7 cm.) occupied its normal site and drained to the right atrium: no valve guarded its orifice. The oblique vein of the left atrium could not be defined. The left atrium, slightly dilated and considerably hypertrophied, received three pulmonary veins, two right and one left. The mitral valve was normal (circumference 8·6 cm.). The right atrium was unusually small and received only the superior vena cava and the coronary sinus. The tricuspid valve was small (circumference 10 cm.) but anatomically normal. The interatrial septum was complete and a probe could be passed neither from the left to the right atrium nor in the reverse direction. Although the fossa ovalis was of normal size, the annulus fossa ovalis was postero-inferior in position (Fig. 5). The crista terminalis could not be identified.

The left ventricular wall was hypertrophied and measured up to 1·8 cm. in thickness except in its posterior part where fibrosis, slight thinning, and aneurysmal dilatation indicated the site of an old healed infarct (Fig. 4). The aorta was perhaps slightly smaller than is usual in a woman of this age (circumference immediately above the aortic valve 8·1 cm.). The aortic valve had three cusps. The coronary arteries, which were entirely free from atheroma, took origin from the anterior and left posterior aortic sinuses. Near the termination of the right coronary artery, at a point corresponding in distribution to the healed infarct, was a limited zone of intimal roughening. The right ventricle was small but the pulmonary artery appeared normal (circumference 8·6 cm.). The ductus arteriosus was obliterated. The condition of the circulation is shown diagrammatically in Fig. 6.

FIG. 5.—The interatrial septum, with the unusual fossa ovalis, the annulus being postero-inferior.

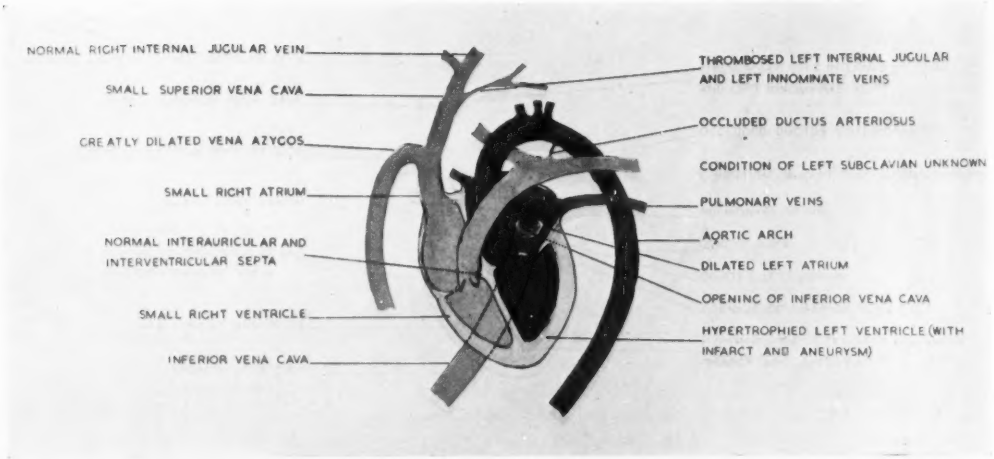
NORMAL RIGHT INTERNAL JUGULAR VEIN
SMALL SUPERIOR VENA CAVA
GREATLY DILATED VENA AZYCOS
SMALL RIGHT ATRIUM
NORMAL INTERAURICULAR AND INTERVENTRICULAR SEPTA
SMALL RIGHT VENTRICLE
INFERIOR VENA CAVA
THROMBOSED LEFT INTERNAL JUGULAR AND LEFT INNOMINATE VEINS
OCCLUDED DUCTUS ARTERIOSUS
CONDITION OF LEFT SUBCLAVIAN UNKNOWN
PULMONARY VEINS
AORTIC ARCH
DILATED LEFT ATRIUM
OPENING OF INFERIOR VENA CAVA
HYPERTROPHIED LEFT VENTRICLE (WITH INFARCT AND ANEURYSM)

FIG. 6.—A diagram of the circulation, showing the inferior vena cava entering the left atrium.

The right lung weighed 500 g. and the left 425 g. The pleural cavity over the anterior border of the left lower lobe was obliterated by fibrous adhesions which covered an area of 2 × 3 cm. Beneath this area was a zone of grey-white tissue, representing an old infarct. The liver (1650 g.) was covered by a smooth capsule, and the arrangement of the hepatic lobes, which were intensely congested, was normal. The spleen was firm and congested (270 g.). At the junction of the inferior and lateral surfaces of the right frontal lobe of the brain (weight 1290 g.) 1 cm. anterior to the lateral fissure, was

a slightly yellow area of cortical softening, 2 cm. in diameter. The cerebral blood vessels were normal and free from atheroma. The right kidney weighed 155 g., the left 160 g. The bone marrow of the right femur was congested through its extent and microscopy revealed erythroid hyperplasia.

Discussion

Very many variations in the developmental pattern of the inferior vena cava have been described, but few of the resulting anomalies are significant causes of congenital heart disease (Taussig, 1947; Brown, 1950; and Schnitker, 1952). Occasionally the left superior and inferior venæ cavæ have been found to drain together into the left atrium, but in these instances the circulation has been maintained by patency of the interatrial septum.

In the case described the principal clinical features were the cyanosis and clubbing of the fingers in the absence of murmurs or cardiac enlargement, and the capacity to lead an active life in spite of repeated pregnancies. She differed from most cyanotic patients with congenital heart disease in that she showed no evidence clinically or radiologically of enlargement of the right ventricle or of generalized cardiac enlargement. Repeated screening also suggested that the left ventricle was within the limits of normal. The cardiogram showed the same changes in limb leads at the age of 22 as at 29. The tendency to embolism was probably the result of her toxæmia of pregnancy and of the infections that followed it. Although the site of origin of the emboli is unknown, both systemic and pulmonary emboli may have originated from the same source.

No diagnosis that would embrace all the findings was made during life. The diagnosis of an atypical Eisenmenger's complex was considered but the combined absence of murmurs and of cardiac enlargement rendered this unlikely. In view of her age when she was first seen further investigations did not appear to be justified, even had the patient been willing. Angiocardiography and cardiac catheterization via the leg veins would appear to be the most likely method of establishing the diagnosis during life in a future case.

The developmental abnormality was confined to the proximal (hepato-cardiac) segment of the inferior vena cava (Hamilton *et al.*, 1945; Arey, 1946), which normally represents the termination of the right vitelline vein (McClure and Butler, 1925) and, in the case described, drained blood to the left side of the heart instead of the right (Fig. 6). Venous blood therefore entered the systemic circulation resulting in constant reduction of the arterial oxygen saturation. The presence of a dilated azygos vein, however, suggests that a significant volume of venous blood may have returned to the right atrium. Both interatrial and interventricular septa were complete but the structure of the fossa ovalis, with the anomalous postero-inferior position of the annulus, cannot be explained.

Summary

A case of cyanotic congenital heart disease without cardiac enlargement or murmurs is described. The patient retained considerable capacity for effort until sudden death occurred at the age of 32 years.

Necropsy revealed a congenital abnormality of the inferior vena cava which drained into the left atrium. No other developmental abnormalities of significance were found.

We wish to thank Professor J. D. Boyd for his advice on the nature of the anatomical abnormality, and Dr. A. M. Barrett for much help with the dissection of the specimen. We are grateful to Miss Sylvia Westoby for the photographs and to Miss Ailsa Muir for the drawings.

This report is based on a communication presented to the British Cardiac Society in April, 1954. The anatomical specimen was demonstrated to the Pathological Society of Great Britain in January, 1954.

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REDISTRIBUTION OF SYSTEMIC BLOOD FLOW IN PULMONARY STENOSIS

BY

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Measurements of blood flow by the direct Fick method at cardiac catheterization have shown that in conditions such as Fallot's tetralogy, the resting systemic flow is within normal limits (Ernsting and Shephard, 1951). In pure pulmonary stenosis the association of a closed ventricular septum with a stenosed valve gives a greater potential restriction of systemic flow, but in practice a large proportion of cases show a resting flow that is within normal limits (Campbell, 1954); and cases with an increased flow through the pulmonary circuit are receiving increasing recognition (Deuchar and Zak, 1952).

Despite the comparative rarity of a reduced systemic flow, it is a fact of clinical experience, recognized since the time of Morgagni (1769), that many cases of pure pulmonary stenosis show evidence of peripheral cyanosis even in the resting state. In the recent series of Campbell (1954), only 15 of 44 cases gave no history of cyanosis; there was good reason to believe that cyanosis was peripheral in type in most of the remaining 29, although in some a potentially patent foramen ovale may have opened under the stress of severe exercise. It must therefore be concluded that there is a selective restriction of blood flow to those sites where cyanosis is commonly observed, particularly the superficial tissues of the extremities.

In the present paper, the discrepancy between the clinical estimates of cyanosis and the calculated systemic blood flow is examined further, and evidence of a possible redistribution of systemic flow is sought by analysis of the oxygen content of the various mixed venous blood specimens obtained at cardiac catheterization.

TECHNIQUE

Cyanosis. The clinical grading of cyanosis is largely that described by Campbell (1948), but the scheme has been amplified to cover the range of peripheral cyanosis. The degrees recognized in the present paper are as follows:

0. No cyanosis at any time.
¼. Occasional cyanosis in cold weather.
½. Consistent cyanosis in cold weather.
¾. Consistent cyanosis in cold weather and sometimes on exertion also.
1. Consistent cyanosis with cold weather and exertion.
2. Cyanosis apparent to trained observer at rest in warm room.
3. Cyanosis easily noticed by patient's friends.
4. Cyanosis gross.

Screening. An attempt has been made to grade pulmonary flow on the findings at fluoroscopy. Previous work by Campbell (1951) suggested that the degree of visible pulsation in the pulmonary

vessels was related largely to the level of pulmonary flow. For the present purpose, note has been taken of the density of the lung fields and the degree of pulsation in the large pulmonary vessels, and four grades of flow have been recognized as follows:

1. Diminished density of lung fields.
2. Normal density of lung fields.
3. Increased pulsation of pulmonary vessels with apparently normal density, or increased density with apparently normal pulsation in pulmonary vessels.
4. Increase of both density and pulsation of pulmonary vessels.

Cardiac Catheterization. The technique of catheterization used in this hospital has already been described (Holling and Zak, 1950). Ninety-four per cent has been accepted as the lower limit for the oxygen saturation of arterial blood, breathing air.

Relationship between Cyanosis and Flow

Peripheral Nature of Cyanosis. Cyanosis has been estimated as indicated above. The figure adopted represents an average value, taking into account the patient's history and a number of examinations both in the out-patient department and in the wards. The relationship between this clinical estimate of cyanosis and the systemic blood flow as measured at cardiac catheterization is examined in Fig. 1. All of the cases illustrated were thought to have pure pulmonary stenosis,

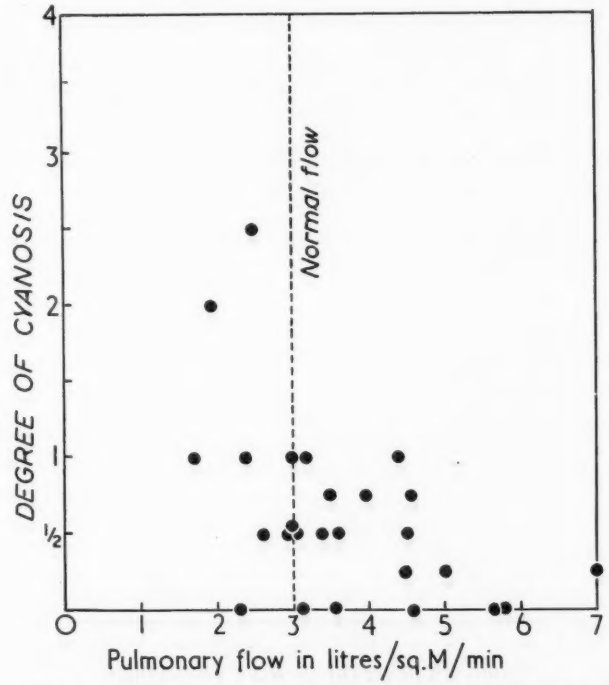

FIG. 1.—*Relationship between level of pulmonary flow and cyanosis in* 26 *cases of pure pulmonary stenosis.* Pulmonary flow measured at cardiac catheterization (direct Fick principle). Cyanosis estimated as described in text. Note that many patients with a normal pulmonary flow show some cyanosis.

and the arterial oxygen saturation was within normal limits.* Any cyanosis that was observed in these patients, at least in the resting state, should therefore be peripheral in type.

The peripheral nature of the cyanosis was confirmed by the evidence of the patients, all except one of whom were certain that cyanosis was precipitated by exposure to cold. In five there was also occasional cyanosis with exertion, and here a temporary shunt through a patent foramen ovale may have contributed to the cyanosis. However, these findings are in marked contrast with the histories given by patients where catheterization confirmed the diagnosis of a right-to-left shunt through a patent foramen ovale, all of the latter group complaining of cyanosis after exertion (in one case—O931, f, 33 years—when she was particularly hot).

Correlation of Cyanosis with Flow Rate measured by Fick method. The lower limit of the normal resting flow calculated by the Fick principle is probably about 3·0 l./sq. m./min. (Cournand, 1945; Stead *et al.*, 1945), and it can be seen that in the present group of pulmonary stenosis cases only 6 of 26 readings fall below the normal level. There is clearly a relationship between the grade of cyanosis and the level of flow, although the degree of correlation is not very close. Of the 6 patients with reduced flow, all except one (P310, m., 21 years) show a significant degree of cyanosis; the low flow rate in this case was a surprise, since he was leading a normal and very energetic life. It is certainly not due to technical errors, since he showed a normal oxygen consumption, and the low saturation of the pulmonary arterial blood was confirmed by two independent observers on different specimens. Further, the right ventricular pressure (systolic 140 mm. Hg) and the electrocardiogram (T wave inversion to V4) confirm the severe nature of the stenosis in his case, and the absence of cyanosis is as yet unexplained.

Of the twenty patients with a normal or increased flow, quite a high proportion show some evidence of cyanosis, twelve being graded as ½–1 degree. It might be thought that this discrepancy was due to a difference of state between the time at which cyanosis was observed and the time when the cardiac output was measured at catheterization, and it must be admitted that in one or two instances where a high cardiac output was recorded, there was some evidence of departure from the basal state, particularly an increase in metabolic rate. However, this is not true of the group as a whole, and typically the metabolic rate is within normal limits (Holling, 1952). Further evidence that the pulmonary flow is not altered by emotional disturbances during catheterization can be obtained by comparing the Fick flow rates with the estimate of flow made on fluoroscopy at out-patients.

Evidence from Fluoroscopy. A comparison of the pulmonary flow, calculated by the Fick principle, and the screening estimate of flow is given in Fig. 2. In general there is a satisfactory correspondence between the two values, suggesting that the level or pulmonary flow at out-patients corresponds with the flow at cardiac catheterization. The most serious discrepancy between screening impressions and calculated pulmonary flow was in a case with a patent foramen ovale (O931, f, 33 years). Here the initial catheterization value (4·8 l./sq. m./min.) was almost certainly erroneously high due to anxiety, and a second catheterization after valvotomy, when the patient admitted to being less nervous, showed that the cardiac output had actually fallen to just below the normal level (2·9 l./sq. m./min.).

Functional Significance of Cyanosis. From the classical work of Lundsgaard and Van Slyke (1923) it is known that at least 5 g. of reduced hæmoglobin per 100 ml. of blood are necessary to produce visible cyanosis. In conditions such as Fallot's tetralogy, where the hæmoglobin level of the blood is increased and there is also a right-to-left shunt, it is not surprising that the threshold for cyanosis is reached. However, where the hæmoglobin level is normal and there is no

* One case (0468, f, 8 years) shows an arterial oxygen saturation which is a little below the accepted normal value (92·2%), and in her case it is possible that a foramen ovale was forced open with exertion, although most of her cyanosis appeared to be peripheral.

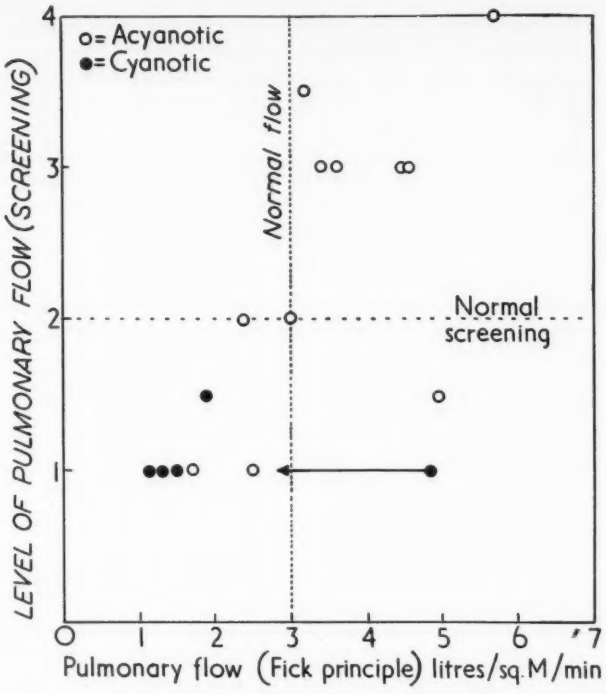

FIG. 2.—*Relationship between screening and catheterization estimates of pulmonary flow in cases of pulmonary stenosis.* In most instances there is a satisfactory correspondence between the two measurements.

intracardiac shunt, cyanosis cannot occur without a considerable reduction in the blood flow to a part. In normal subjects this may sometimes occur in the extremities in severe cold weather, and it has been suggested that in these circumstances a variation in calibre of the arterio-venous shunts (Grant, 1930) reduces the blood flow to the limbs in order to conserve body heat. It would seem that a similar mechanism operates in pulmonary stenosis, since in such cases the cyanosis is worse in cold weather; however, in many instances the sensitivity of this shunting mechanism appears to have been altered so that cyanosis appears at more normal external temperatures. The advantage of such an arrangement to the body economy has already been pointed out (Campbell, 1954). Although the resting cardiac output is usually within normal limits, in many cases of stenosis the right ventricular pressure is nearing a limiting value, so that during exercise little increase in systemic flow is possible. A limitation of blood flow to less vital areas of the body probably serves to conserve the limited cardiac reserve, and guards the more important organs from oxygen want under the conditions of exercise.

EVIDENCE OF REDISTRIBUTION OF CAVAL FLOW

It was decided to test the hypothesis of a selective redistribution of blood flow by analysing the relative flow rates in the superior and inferior venæ cavæ of a group of pulmonary stenosis cases submitted for cardiac catheterization.

In a normal person, the oxygen saturation of blood samples taken from the superior vena cava

is about 4 per cent less than the saturation of samples obtained from the inferior vena cava, and the composition of mixed venous blood can be explained by the mixing of these two streams in the ratio 2 : 3 (Hultgren *et al.*, 1953). If an increased proportion of the systemic flow is directed to the head, the superior vena caval sample should reveal this change by a saturation approximating more closely to the mixed venous level, while the inferior vena caval sample should diverge more widely than normal from the mixed venous value.

Thirty-eight cases of pulmonary stenosis have been examined from this point of view—26 with pure pulmonary stenosis and 12 with patent foramen ovale. For purposes of comparison, a group of 16 cases of patent ductus arteriosus has been subjected to similar analysis: in this group the arterial saturation and resting systemic flow are normal, and there should be a more normal capacity to vary flow with exercise.

Estimation of " Mixed Venous " Oxygen Saturation. The first problem to settle is which of the various blood samples gives a reliable indication of the saturation of mixed venous blood. There is some evidence of laminar flow in the right atrium (Holling and Zak, 1950; Sirota and Gordon, 1954), and although the present results do not reveal this in terms of a systematic difference between the atrial and ventricular samples or in a larger standard deviation for the oxygen saturation of atrial samples (Table I), it has been thought wiser to limit the estimation of mixed venous saturation to values derived from the right ventricular and pulmonary arterial samples.

TABLE I

AVERAGE OXYGEN SATURATION OF RIGHT ATRIAL, RIGHT VENTRICULAR, AND PULMONARY ARTERIAL BLOOD SPECIMENS, WITH ESTIMATE OF STANDARD DEVIATION OF SINGLE OBSERVATION IN EACH GROUP

Diagnosis	Saturation of R.A. samples (percentage)	Saturation of R.V. samples (percentage)	Saturation of P.A. samples (percentage)
Pure pulmonary stenosis	68·3 $S_d \pm 8{\cdot}5$	67·8 $S_d \pm 9{\cdot}3$	68·0 $S_d \pm 8{\cdot}6$
Pulmonary stenosis with patent foramen ovale	55·6 $S_d \pm 14{\cdot}5$	56·0 $S_d \pm 11{\cdot}3$	49·9 $S_d \pm 20{\cdot}4$
Patent ductus arteriosus	69·4 $S_d \pm 7{\cdot}6$	70·5 $S_d \pm 6{\cdot}4$	Increased by left-to-right shunt

In severe pulmonary stenosis, the saturation of the pulmonary arterial specimen may be much lower than a specimen withdrawn simultaneously from the right ventricle, and this has been attributed to material obstruction of pulmonary flow by the catheter tip. Five of the present series appear to fall into this category (Table II), although the group as a whole shows no significant difference between right ventricular and pulmonary arterial samples. Thus in these five cases it

TABLE II

DIFFERENCE IN OXYGEN SATURATION BETWEEN RIGHT VENTRICLE AND PULMONARY ARTERY IN FIVE CASES OF PULMONARY STENOSIS WITH LOW RESTING PULMONARY FLOW

Case No.	Sex and age	Pulmonary flow (l./sq. m./min.)	Saturation of R.V. sample (percentage)	Saturation of P.A. sample (percentage)	Difference P.A.–R.V. (percentage)
O328	F 13	1·9	49·2	40·5	− 8·7
O468	F 9	2·4	53·5	33·4	−20·1
P288	F 6	2·2	61·1	48·0	−13·1
O745	F 19	3·2	52·3	43·3	− 9·0
O207	F 26	2·2	47·2	22·1	−25·1

has been necessary to take the right ventricular samples alone as indicative of mixed venous saturation. In patent ductus arteriosus a similar procedure is necessary on account of the shunt into the pulmonary artery.

Changes in Caval Flow. Having decided upon the mixed venous oxygen saturation in this way, it is possible to measure the deviations of superior and inferior vena caval samples from the mixed venous value, and to compare the deviations with those expected on a 2 : 3 flow ratio. It can be seen (Table III) that in patent ductus arteriosus, the difference from the expected value is no greater

TABLE III

DEVIATIONS OF OXYGEN SATURATION OF SUPERIOR AND INFERIOR VENA CAVAL SPECIMENS FROM SATURATION OF MIXED VENOUS BLOOD—A STATISTICAL COMPARISON WITH VALUES EXPECTED ON A 2 : 3 FLOW RATIO IN GREAT VEINS

Diagnosis	Sample	Number of cases	Deviation from M.V.B (percentage)	Expected deviation (percentage)	Difference (percentage)	Probability
Pure pulmonary stenosis	S V.C. I.V.C.	26 26	−0·02 +4·21	−2·54 +1·69	+2·52 s.e.±0·71 +2·52 s.e.±1·17	0·001–0·01 0·05–0·02
Pulmonary stenosis with patent foramen ovale	S.V.C. I.V.C.	12 12	−3·90 +4·69	−5·16 +3·43	+1·26 s.e.±2·28 +1·26 s.e.±1·50	0·5–0·7 0·5–0·3
Patent ductus arteriosus	S.V.C. I.V.C.	16 16	−1·38 +2·88	−2·56 +1·70	+1·17 s.e.±1·15 +1·17 s.e.±2·14	0·3 0·5–0·7

than could be explained on a chance variation (thus for the S.V.C. sample P=0·3). However, in pure pulmonary stenosis, the departure from expectation is much larger, and of considerable significance (for the superior vena caval sample P is in the range 0·01–0·001). Thus it is clear that in this condition the upper half of the body receives an unusually large proportion of the systemic blood flow. It is perhaps rather surprising that this finding is not repeated in pulmonary stenosis with a patent foramen ovale, for if anything the systemic flow in this group is smaller. However, it is possible that here oxygen differences are disturbed by the diversion of a proportion of caval flow to the left atrium.

DISCUSSION

The above analysis gives clear evidence that in pure pulmonary stenosis the systemic blood flow shows an abnormal distribution, an increased proportion of the cardiac output reaching the upper half of the body. Further, it seems probable that this represents mainly an increase of flow to the head, since the arms and hands show a high incidence of peripheral cyanosis.

The importance of this redistribution during exercise has already been discussed. The degree of adaption which can be achieved by this mechanism is uncertain, but it is of some significance that whereas in Fallot's tetralogy hæmodynamic instability and other signs and symptoms of medullary hypoxia may appear during exercise (Shephard, 1954), in pulmonary stenosis such attacks are rare. Calculation of the mean systemic capillary oxygen tension (Houston and Riley, 1947; Ernsting and Shephard, 1951) reveals that the *average* degree of tissue hypoxia is very similar in the more severe forms of either condition, and the absence of attacks in pulmonary stenosis supports the view that a more favourable oxygen tension is maintained in the medullary centres by selective redistribution of the available cardiac output.

Summary

Pure pulmonary stenosis shows a high incidence of peripheral cyanosis, but despite this the cardiac output as measured by the direct Fick method at catheterization is typically within normal limits. Analysis of the caval blood samples in 26 cases of pure pulmonary stenosis, 12 cases of pulmonary stenosis with patent foramen ovale, and 16 cases of patent ductus arteriosus shows that in pure pulmonary stenosis the blood flow from the upper half of the body exceeds the normal value of 40 per cent of the cardiac output. The mechanism and importance of this redistribution during exercise are briefly considered.

I am greatly indebted to Dr. Campbell, who provided the data relating to screening and cyanosis from his personal records, and gave much helpful criticism in the preparation of this paper. My thanks are also due to the Department of Medical Illustration for their cooperation in producing the diagrams.

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CASE REPORTS

CONTINUOUS VENOUS HUM IN A CASE OF PORTAL CIRRHOSIS

BY

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Venous hums to be heard on auscultation over the epigastrium in cases of portal cirrhosis were described more than a hundred years ago by Pégot (1833) and by Cruveilhier (1835), and early in this century by Baumgarten (1908). Hanganutz (1922) collected six cases all of which presented a small cirrhotic liver, portal hypertension, a venous anastomosis in the falciform ligament and abdominal wall connecting the portal and the epigastric veins and a bruit or hum audible over the epigastrium and lower end of the sternum. He believed this syndrome to be a separate clinical and pathological entity and applied to it the name Cruveilhier-Baumgarten cirrhosis. Armstrong *et al.* (1942) reviewed the cases published to that date and divided them into two groups. The first consisted of young people in whom there was atrophy of the parenchyma of the liver, but little or no fibrosis, and a large patent vein which joined the left portal vein to the abdominal parietal veins by way of the free margin of the falciform ligament. Armstrong and his colleagues believed that this was the umbilical vein and that its congenital patency was the primary abnormality in these cases, the changes in the liver being secondary to the deprivation of portal blood. They considered these cases to be examples of Cruveilhier-Baumgarten cirrhosis. In the second and much larger group, which they referred to as the Cruveilhier-Baumgarten syndrome, no congenital anomaly was present. The primary condition was hepatic cirrhosis with associated portal hypertension. Partial recanalization of the obliterated umbilical vein occurred in some patients and in others enlargement of the para-umbilical veins (Sappey, 1889) and of the connections between them and the epigastric veins. Two further instances have since been described by Bloom (1950).

In normal development the umbilical vein is obliterated a few days after birth, but its connection with the left branch of the portal vein and its proximal (hepatic) end frequently remain patent. According to Segall (1923) it was patent for variable distances up to two-thirds of its length in 19 of the 55 specimens he examined. This "Restkanal" (Baumgarten) may in turn communicate with the epigastric veins through the small veins of Burow (1838). The anastomosis is of no significance in the healthy individual, but assumes importance as part of the collateral circulation should portal hypertension develop. In describing three cases seen at necropsy Butler (1952) indicated that this form of portal-epigastric anastomosis varied greatly in size, in one instance the lumen of the replacing vein being so large that it could only be distinguished from a congenitally patent umbilical vein by the histological structure of its wall.

The following case is presented as an example of the Cruveilhier-Baumgarten syndrome in which the cirrhosis and portal-epigastric anastomosis were associated with gross ascites. A venous hum was heard in the epigastrium and was recorded with the phonocardiograph.

Case Report

A single woman, aged 73, was admitted to the charge of Dr. W. I. Card in the Western General Hospital, Edinburgh, with a short history of weakness, dyspnœa on exertion, ankle swelling, and loss of weight. Most of the patient's life had been spent in the Dutch West Indies, where she had always been healthy. A small consumption of alcohol was admitted. In 1948 chronic cholecystitis was diagnosed on the basis of mild dyspepsia and a non-functioning gall-bladder. There was no history of other illness.

Physical Examination. Temperature and pulse and respiration rates were normal. The patient was very thin. Although there was no jaundice, the skin was dry and pigmented, and showed a widespread psoriasis. The hands presented "liver palm" appearance, but no finger clubbing. Apart from mental confusion, no abnormality of the central nervous system could be detected. There were scanty basal crepitations, but no venous congestion or peripheral œdema, and in other respects the cardiovascular system was normal. A moderate ascites was present and the liver edge was just palpable. On auscultation over the epigastrium and lower sternum, a curious humming bruit could be heard. Rectal examination revealed only the presence of small hæmorrhoids.

Laboratory Findings. Urine contained a trace of urobilinogen but no bile or other abnormality. Fæces were normal in appearance; no occult blood was detected. Blood: Hb. 94 per cent, W.B.C. 4,000 per c.mm., E.S.R. 45 mm./hr.; plasma proteins, total 6·75 g. per 100 ml. (albumin, 3·20, globulin 3·55); serum bilirubin 0·9 mg. per 100 ml.; alkaline phosphatase 16 units (King); cephalin cholesterol flocculation +(4); blood urea nitrogen 12 mg. per 100 ml. Electrocardiogram normal. There was a histamine-fast achlorhydria. X-rays of the chest showed no abnormality; films of the abdomen (erect) showed moderate distension of the bowel with several fluid levels and evident ascites; barium swallow revealed extensive œsophageal varices.

Progress. On the third day after admission the patient lapsed into a coma which lasted four days. She made a complete recovery and over the succeeding four months showed no tendency to relapse, but the ascites increased and gross peripheral œdema appeared. Paracentesis abdominis was performed on nine occasions with a total withdrawal of 40 litres of fluid. Repeated injections of mercurial diuretics were given with varying but never very good response. High protein diet with oral hepovite and supplementary vitamins was not well tolerated. There was a low grade intermittent fever and the patient complained of occasional right-sided abdominal pain, which was relieved by analgesic tablets. Five months after admission her condition began to deteriorate, progressive weakness and muscle wasting developed and the response to mercurial diuretics became progressively smaller. For three weeks before death she was comatose and took no food or drink. She died in a state of gross inanition with massive ascites and peripheral œdema.

The Murmur. The murmur was heard on auscultation over the epigastrium, the medial third of both costal margins and over the sternum as far up as the third costal cartilage. It was maximal on either side of the xiphoid cartilage, was heard in all phases of respiration and did not vary with posture. It resembled the murmur of a patent ductus arteriosus in that it was continuous throughout systole and diastole, and varied slightly in intensity and pitch with the cardiac cycle. In character the murmur was a soft-pitched hum not unlike the noise of wind blowing through telegraph wires, and conformed to the original description of a venous hum given by Laennec (1819), who likened it to the sound of the "sea or that produced by the application of a large shell to the ear." There was no palpable thrill. Although no large subcutaneous

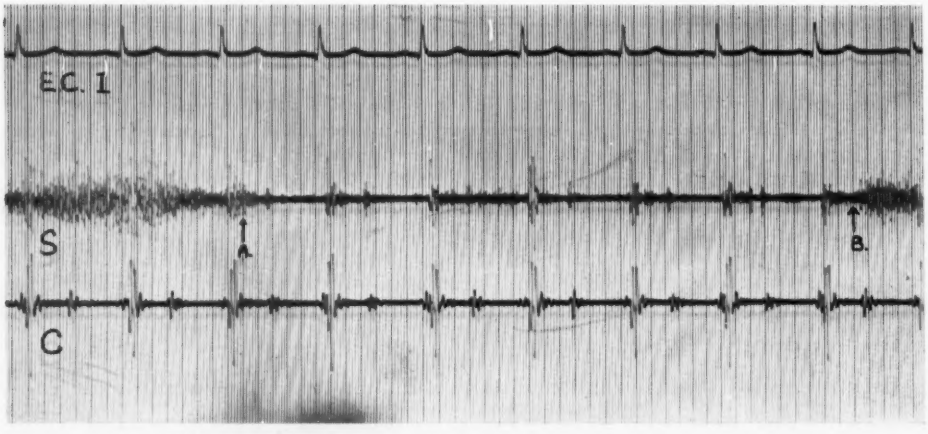

FIG. 1.—Continuous venous hum in hepatic cirrhosis. Simultaneous recordings of electrocardiogram (lead I) and phonocardiograms at lower end of sternum (S) and at cardiac apex (C); (A) light pressure applied with hand on epigastrium; (B) pressure released.

veins were visible above the umbilicus the murmur disappeared when light digital pressure was applied across the epigastrium in the mid-line and reappeared immediately pressure was released.

Two synchronous phonocardiograms were recorded (Fig. 1), one from a point just over the lower end of the sternum where the murmur was loudest and a second simultaneous tracing from the cardiac apex to show the normal heart sounds. At the point on the tracing marked " A " gentle pressure applied with the edge of the hand across the epigastrium caused the murmur to disappear. When pressure was released, at the point " B " on the tracing, the murmur reappeared.

A series of vibrations can be seen to persist in the sternal tracing when pressure was applied. The regular vibrations coincide with the normal heart sounds as recorded at the apex and are in fact the heart sounds which are conducted from the præcordium and only become apparent in the epigastrium when the venous hum is obliterated. The irregular high frequency vibrations represent the breath sounds, the patient being unable to breathe quietly or hold her breath while the recording was being made.

Necropsy showed the presence of gross hepatic cirrhosis. The gall-bladder contained a single mixed stone with a cholesterol nucleus and was the seat of suppurative cholecystitis with localized abscess formation. There was a massive ascites and œdema of all the connective tissue spaces. The heart was normal and the lungs were congested. The microscopical appearance of the liver showed extensive fibrosis and complete replacement of the normal lobular architecture by areas of nodular hyperplasia.

The venous anastomosis was demonstrated after death by injection into the superior mesenteric vein of a solution of 1 per cent methylene blue and 12 per cent potassium iodide. A drawing of the dissected specimen is shown in Fig. 2. The round ligament was unusually large and was so stained by the methylene blue that in the naked-eye specimen it seemed that complete recanalization must have occurred. Only the hepatic end of the umbilical vein was in fact patent. As it entered the free edge of the falciform ligament the single lumen disappeared and its place was taken by innumerable small channels in and around the round ligament which in other respects showed a normal adult structure. From this portion of the round ligament one moderate sized and several small veins communicated with a dilated and tortuous vein which ran cephalad in the extra-peritoneal tissues. At the distal (umbilical) end of the round ligament there were,

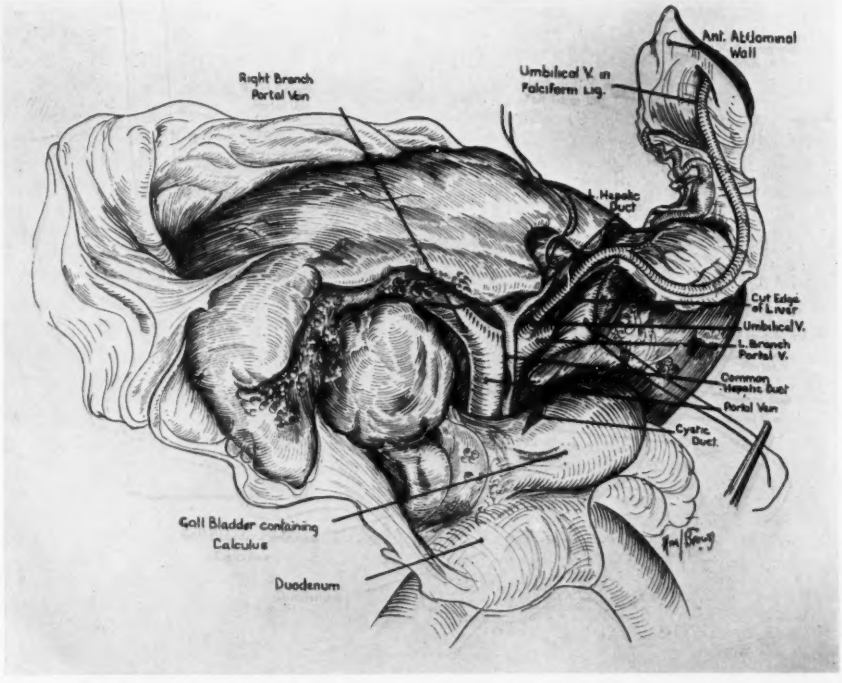

FIG. 2.—Drawing of the specimen removed at necropsy to show the portal-epigastric anastomosis along the falciform ligament.

in addition to the para-umbilical veins, small vessels within the ligament approximately 0·5 mm. in diameter and with relatively thick walls, which consisted largely of fibrous tissue. A lateral radiograph demonstrated that the opaque medium had traversed the portal-epigastric anastomosis observed in the necropsy specimen and had entered the internal mammary veins in the retro-sternal plane.

Discussion

Portal-systemic venous connections in portal hypertension have been classified as (1) dangerous or vulnerable, and (2) protected or beneficial anastomoses (McNee and Macpherson, 1952; Butler, 1952). The first group comprises the varices at the lower end of the œsophagus and in the fundus of the stomach which by reason of their exposed position are liable to rupture and to give rise to the hæmorrhages which are characteristic of this condition. The second group includes the retro-peritoneal anastomoses, enlargement of intra-muscular and intra-neural vessels (such as those described by Butler (1952) within the vagus sheaths) and the veins in the hepatic and falciform ligaments. The presence of these connections is entirely beneficial, but for the most part they are of such small calibre that it takes many thousands of them to compensate for the obstruction to flow through one large vessel. A postero-anterior radiograph demonstrated this point in the present case, showing that the portal-epigastric anastomosis was of small size and of little practical importance in comparison with the collateral circulation which had developed in relation to the left gastric vein.

It is not possible to determine exactly the site of origin of the murmur in this case. According to Lutembacher (1936) the murmur arises where a small vein enters a dilated one, for example at the junctions of the para-umbilical veins with the dilated and tortuous epigastric veins. The disappearance of the sound on light pressure over the epigastrium would be compatible with this explanation. On the other hand the maximum intensity of the bruit in the region of the xiphisternum suggests that it may originate in turbulence occurring at the junction of the left portal and umbilical veins. The disappearance of the sound on pressure over the epigastrium could then be accounted for by the cessation of flow into the patent end of the umbilical vein. Observations made by McFadzean and Gray (1953) provide some support for this view. In five out of nine cases of hepatic cirrhosis they reported that a venous hum was not audible over the epigastrium but was detected on direct auscultation of the liver and became progressively louder as the porta hepatis was approached. Large veins were demonstrated in the falciform ligament in three of these cases. In another case which they reported in detail they concluded that the murmur originated in arterio-venous communications within the liver and was conveyed directly to the abdominal wall. That this was not the mechanism of its production in the present case is suggested by the fact that the murmur disappeared when light pressure was applied to the epigastrium.

Summary

A case of hepatic cirrhosis and portal hypertension in which a bruit could be heard in the epigastrium is described. The phonocardiogram made during life is presented together with a drawing of the anastomosis made at necropsy. A venogram was also made after death.

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EBSTEIN'S ANOMALY:

REPORT OF A CASE DIAGNOSED DURING LIFE

BY

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The congenital malformation and displacement of the tricuspid valve described by Ebstein nearly a century ago is rare; less than 50 cases have been reported, many of them recently. Yater and Shapiro (1937) considered a clinical diagnosis to be impossible, but Engle *et al.* (1950) indicated the criteria for such a diagnosis: briefly these were gross enlargement of the right heart with decreased pulsation, decreased vascularity of the lungs, right bundle branch block, and delayed A-V conduction. Cardiac catheterization was regarded as a useful aid by Reynolds (1950) and by Broadbent *et al.* (1953). Soloff *et al.* (1951) made the diagnosis chiefly on the angiocardiogram. Blacket *et al.* (1952) reported 5 cases in one of which " the diagnosis has been confirmed at autopsy," but it is not clear whether the diagnosis was definite or on what evidence it was made before the fatal catheterization.

Case Report

In the present case the diagnosis was made during life and was confirmed post mortem eleven weeks later.

An 18-year-old man was referred for cardiac investigation. No detailed history of his early life was available. The patient led a normal active life except that extreme effort would result in dyspnœa and fatigue. Exercise such as swimming produced cyanosis but usually his colour was ruddier than that of the average person.

His height was 5 feet 5 inches and weight 120 lb. and his muscle and chest development were normal. His cheeks, lips, and ears were unusually florid and there was no cyanosis. A systolic murmur was heard with maximum intensity in the third and fourth left interspaces near the sternum and was propagated to the apex and base. The heart rate was 70 a minute and regular in rhythm and the blood pressure was 126/80. Clubbing of fingers and toes was absent. Physical examination was otherwise essentially normal.

The electrocardiogram showed low voltage in the limb leads and the QRS duration was 0·16 sec. The chest leads were remarkable. V3R and V1 showed a deep fast Q and a slow late R indicating right bundle branch block. Between V1 and V2 there was an abrupt change to a small R and tall R1 followed by a slightly negative and then a positive peaked T wave. In the V4 position the T wave became deeply negative. At V5 there was another abrupt change, the QRS decreasing greatly and becoming tent-shaped. At V6 an early tall R wave was followed by a slow wide S wave. The P-R interval was 0·17 sec. and the P vector pointed upward and to the left in the frontal plane. In leads I and V1 the P was broad and slightly notched. The cardiogram was interpreted as showing chiefly right ventricular events as far to the left as the V4 position. Position V5 was probably just to the right of the transition zone, while V6 was the first position to show left ventricular events.

X-ray report (Fig. 1) (Dr. L. R. Harnick): " The heart is globular in shape and is enlarged with a cardiothoracic ratio of 17·5 to 29 cm. There is a striking avascularity of the lung fields and the hilar vessels as well as the pulmonary trunk are greatly reduced in size. The arch of the aorta is small but probably normal. In the lateral film there is marked enlargement anteriorly, the appearance being consistent with right ventricular enlargement."

On cardiac catheterization, the right atrium seemed very large; a ventricular type of pressure curve was not obtained until the tip of the catheter was far to the left of the mid line and nearly to the left border of

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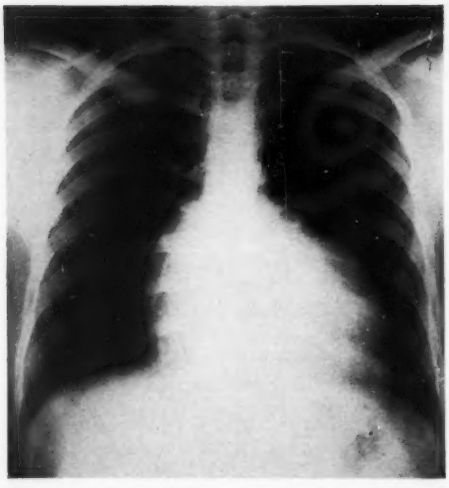
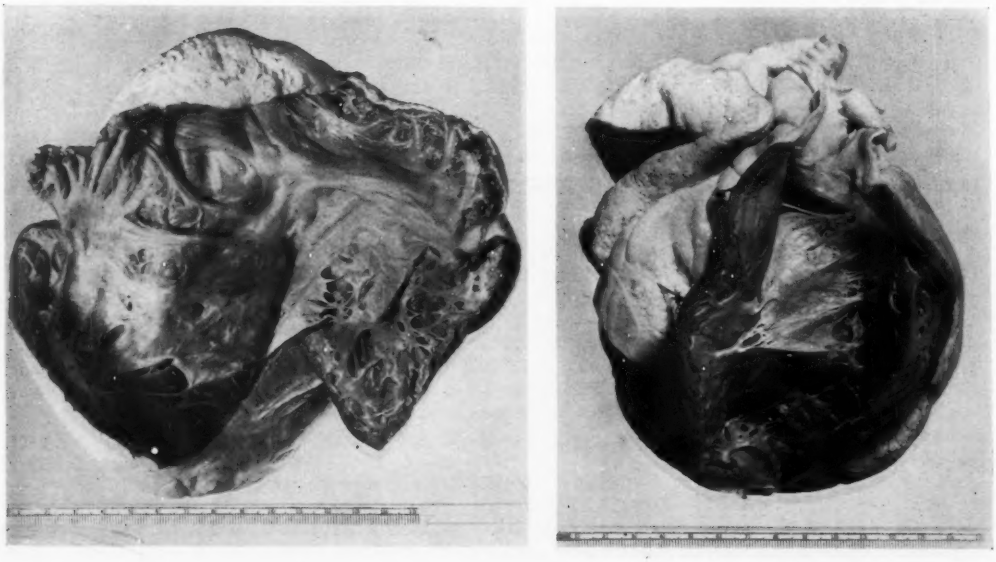


FIG. 1.—Roentgenogram of the heart in the postero-anterior view. Note the marked decrease in the vascularity of the lung fields.



A B

FIG. 2.—(A) Heart opened to show the right atrium and the large membraneous sheet of the tricuspid valve attached to the wall of the right ventricle. (B) Heart opened to show the outflow tract and pulmonary valve, as well as the tricuspid malformation.

the heart. The catheter could not be made to turn up into the pulmonary artery. The pressure in the right ventricle was slightly raised (32/6 mm. Hg) as were also those of the right atrium (16/10 mm.), the superior vena cava (20/11 mm.) and the inferior vena cava (16/10 mm.). There was no evidence of an arterio-venous shunt, the oxygen saturations in the right ventricle, right atrium, superior and inferior venæ cavæ being 13·7, 14·4, 13·7, and 14·2 vol. per cent respectively. The moderate femoral artery unsaturation (86%) was attributed to a veno-arterial shunt which was wrongly thought to be through a small atrial septal defect although the catheter had not been passed into the left atrium. On the basis of the very large right atrium, the apparent displacement of the tricuspid valve to the left, and the avascularity of the lung fields, a diagnosis of Ebstein's anomaly was made.

Eleven weeks later after swimming about half a mile, he died suddenly.

Autopsy Report (Dr. W. S. Alexander). Upon opening the chest cavity there was very extensive dilatation of the heart so that the heart itself occupied more than half of the thoracic cavity. This was due entirely to tremendous dilatation of the right auricle and ventricle. The weight of the formalin fixed heart was 400 g.

Examination of the right atrium (Fig. 2A) showed extreme dilatation, both of the atrium and auricular appendix with muscle hypertrophy of the walls of both chambers. The muscle showed extensive trabeculation. The tricuspid valve structure was grossly abnormal. Instead of a recognizable tricuspid valve, there was a membraneous sheet encircling the A-V orifice. This sheet was attached to the A-V ring in a somewhat irregular fashion, but the major abnormality was at its free margin, which was attached by a number of strong thin tendinous cords to the wall of the ventricle quite close to the apical region, so that the valve substance lay as a drape from the A-V orifice almost to the apex of the very greatly dilated right ventricle. There were numerous perforations of this drape, both close to its point of attachment at the base and at the apex.

The right ventricle was grossly hypertrophied and extremely dilated (Fig. 2B). The hypertrophy involved not only the wall of the heart but the columnæ carneæ and the hypertrophied columns extending up behind the fixed valve substance. The wall of the right ventricle proximal to the insertions of the tricuspid valve measured between 7 and 8 mm. in thickness while that of the distal portion, the outflow tract, varied from 4 to 5 mm. There was no free communication between the cavity of the ventricle and pulmonary artery since the valve drape covered the region of the infundibulum. There was moderate dilatation behind the infundibulum and it would appear that much of the blood that escaped from the pulmonary artery reached the infundibulum through the perforations of the sheet of fibrous tissue. The pulmonary valve itself showed no evidence of stenosis. The pulmonary artery was smaller than average size. The ductus arteriosus was well closed.

In comparison with the huge right atrium and grossly dilated appendix, the left atrium was a tiny chamber and the appendix was a very small structure projecting from the surface of the heart. The mitral valve was normal in appearance and led to a left ventricle which, in comparison with the grossly dilated right, was a small structure. The thickness of the muscle, however, was within normal limits for his age and development. The aortic valves were normal in appearance. The aorta itself, however, was smaller than usual and the diameter was considerably reduced. The coronary vessels showed an apparently normal pattern and appearance.

Examination of the interatrial septum showed no evidence of a septal defect. The interventricular septum showed in the region of the pars membranacea septi a pouch, the orifice of which presented on the left ventricular surface of the septum while the pouch itself projected into the right ventricle behind the fibrous sheet of the tricuspid valve. As far as could be determined on gross inspection, there was no perforation of this structure. The ventricular surface on the right side, however, was grossly irregular with thick and thin areas alternating.

The rest of the autopsy showed nothing of significance.

Discussion

The pathology and abnormal physiology of this condition have been discussed at some length by Engle *et al.* (1950), Baker *et al.* (1950), Blacket *et al.* (1952), Broadbent *et al.* (1953), and Edwards *et al.* (1953) and will not be detailed here. There is one point worthy of note. Engle *et al.* (1950) remarked that, "Thinness of the right ventricular wall proximal to the valve has been noted in nearly all the recorded cases," and in each of their three cases this condition obtained. In the only autopsied case among the five seen by Blacket *et al.* (1952) the muscle of both the proximal and distal portions of the right ventricle was thin but "very similar." Engle *et al.* (1950) postulated that some defect of the visceral cœlomic wall destined

to give rise to the right ventricular myocardium might account for the maldevelopment of the muscle and the malformation of the tricuspid valve. However, Edwards (1953) pointed out that one of his cases failed to show atrophy, perhaps because the patient was only two months old. He suggested the possibility that the atrophy might be secondary to the altered dynamics.

In the present case, the wall of the proximal portion of ventricle was thicker than normal while that of the distal portion was slightly if at all increased. This fact would indicate that a visceral cœlomic defect is not an integral part of the deformity. Presumably an unusual degree of tricuspid stenosis would account for the proximal hypertrophy. In this case the altered dynamics were not such as to produce atrophy even over a period of 18 years. It is none the less clear that the output of the right heart was subnormal as indicated by the decreased vascularity of the lung fields.

A noteworthy feature of the pressures at catheterization is the tendency for these to be about the same in the right ventricle and right atrium as shown by Broadbent *et al.* (1953). Perhaps this is due to some degree of tricuspid regurgitation though signs of right-sided passive congestion are usually lacking. The present case failed to show this tendency to equalization of the pressures in the atrium and ventricle. No doubt the variability in the type of deformity produces abnormalities in the dynamics that differ considerably from case to case.

Practically all cases show right bundle branch block and some have prolonged A-V conduction as well. These findings have been attributed by Engle *et al.* (1950) to the dilatation and thinning of the right atrium and proximal right ventricle. This explanation is scarcely tenable in this patient who showed hypertrophy of both these chambers as well as an extreme degree of right bundle branch block.

Two authors (Blacket *et al.* and Campbell) have reported sudden death occurring during catheterization, and in another case it happened during the induction of anæsthesia before thoracotomy (Broadbent *et al.*, 1950). This so far unexplained hazard may be related either to anæsthesia or to the trauma of catheterization, possibly through the production of an arrhythmia. Sudden death occurred in the present case apparently as a result of physical effort. Because of the liability to unexpected death, cardiac catheterization should in most cases be avoided, since the clinical diagnosis can now be made with reasonable assurance, chiefly on the basis of the X-ray appearance.

Summary

A case of Ebstein's anomaly is reported in which the diagnosis was made during life and confirmed post mortem. The diagnosis was based on the X-ray appearance and the very large size of the right atrium at catheterization. The pressure differences between the right atrium and ventricle were well marked, unlike some cases reported in which the two pressures were similar.

Anatomically this case was also different in that the musculature of the right atrium and proximal right ventricle was hypertrophied and not atrophied as is usually the case. There was no atrial septal defect though this is commonly present in Ebstein's anomaly.

It is emphasized that sudden unexpected death occurs during anæsthesia, catheterization, or exercise in these patients. Catheterization should be done only if the clinical diagnosis is in doubt. A reasonably accurate clinical diagnosis can be made on the radiological and the electrocardiographic findings, and is important because no surgical treatment can be offered at present and exploration may be dangerous.

I am indebted to Dr. M. Israels and Dr. Gordon Murray for permission to publish this case, to Dr. W. S. Alexander for the autopsy report, and to Dr. J. D. Stephen for making the specimen available for examination.

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PULMONARY ARTERY THROMBOSIS FOLLOWING CARDIAC CATHETERIZATION

BY

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Major thrombosis of a primary division of the pulmonary artery does not appear to have been recorded as a complication of cardiac catheterization. It therefore seems desirable to record the following case of mitral stenosis in which thrombosis of the right main branch of the pulmonary artery followed catheterization.

Case Report

A 33-year-old housewife was admitted to the Manchester Royal Infirmary under the care of Professor Bramwell, suffering from chronic rheumatic heart disease with mitral stenosis, auricular fibrillation, and congestive heart failure which responded to medical treatment. Cardiac catheterization was performed four weeks after admission. On arrival in the theatre the patient had a rapid auricular fibrillation but her general condition was satisfactory. A No. 8 catheter introduced into the left median cubital vein passed easily to the right main branch of the pulmonary artery where the resting mean pressure was over 78 mm. of mercury. The catheter was then advanced to the wedge position in the right mid-zone where a mean pressure of 24 mm. mercury was recorded. Due to technical difficulty with the saline manometer, it remained in this position for 29 minutes, apart from a short period of withdrawal into the pulmonary artery to test the catheter's patency. Pressure readings and blood samples were taken during withdrawal. Throughout the procedure a slow drip of $\frac{1}{2}$ per cent procaine saline containing 46,000 units heparin/litre was given. All manipulation was under radioscopic control. Five hours after catheterization the patient became dyspnœic and cyanosed, the tachycardia persisting. Following treatment she regained her usual state within 36 hours and her condition remained unchanged until mitral valvotomy was performed three weeks after catheterization. Splitting of the commissure presented no difficulty, but spontaneous respiration was not re-established and the patient died six hours after operation.

Autopsy

The heart weighed 450 g., the right ventricle being dilated and hypertrophied and the left auricle dilated. The pericardial sac contained a few ml. of blood-stained fluid. The cusps of the mitral valve were opaque and thickened and the chordæ tendineæ shortened. The anterolateral commissure had been split so that the valve admitted two fingers. The tricuspid orifice was dilated, admitting five fingers; the valve cusps were healthy. The pulmonary and aortic valves were normal. In the right branch of the pulmonary artery was a firm ante-mortem thrombus, 8 cm. in length and 2 cm. in diameter (Fig. 1). The thrombus had a firm linear attachment, 4 mm. wide, to the posterior wall of the pulmonary artery for a distance of 6 cm; the proximal 2 cm. of the thrombus was free in the lumen, projecting into the main pulmonary trunk at its bifurcation. The lumen of the artery was patent, though much reduced in this region. The intima was moderately atheromatous. The lungs were congested and œdematous. The left lung was partially collapsed and the left pleural sac contained a little blood-stained fluid. No infarcts were present and there was no thrombosis of the smaller arteries. Chronic venous congestion was present in the liver, spleen, and kidneys. The other organs were normal.

Histology

Sections taken through the thrombus and pulmonary artery (Fig. 2) showed the thrombus firmly united to the thickened intima of the artery; there were many dilated capillaries in the adventitia of the vessel. The thrombus contained many fibroblasts and young capillaries, penetrating to a depth of 2 mm., and judged by the degree of organization appeared to be about 3 weeks old.

FIG. 1.—Thrombus in the right main branch of the pulmonary artery.

FIG. 2.—Photomicrograph showing the organizing thrombus and the thickened intima of the pulmonary artery.

Discussion

The evidence suggests that thrombosis of the right main branch of the pulmonary artery was the sequel of cardiac catheterization. Coincidental spontaneous thrombus formation (Billings, 1921; Brenner, 1935) is a possibility, but the site and shape of the thrombus, its age, and the demonstration of patency of the right pulmonary artery at the time of catheterization are against this explanation. Experimentally, endocardial lesions have been found following catheterization in dogs (Ellis *et al.*, 1950; Goodale *et al.*, 1947), but similar lesions in the pulmonary artery do not appear to have been described. Goodwin (1953) records a fatal case of subendocardial hæmorrhage in the right ventricle and postulates the occurrence of similar non-fatal lesions in other cases. Edwards *et al.* (1953) report the case of a patient dying 24 hours after catheterization from cardiac failure secondary to mitral stenosis, who showed a fibrinous deposit in the main stem of the pulmonary artery, probably overlying an endothelial erosion; this may represent an earlier stage of the lesion described in the present case. In mitral stenosis the atheromatous state of the pulmonary artery and its branches would predispose to minor endothelial damage by a catheter or its tip.

Although conditions are not strictly comparable, it seemed worth while to catheterize cadavers in order to discover the possible sites of damage to the pulmonary artery during cardiac catheterization. In passing the catheter to the wedge pressure position considerable buckling occurs, and, according to the position of the terminal artery catheterized, the buckled catheter may press on the

superior, posterior, or anterior wall of the main stem pulmonary artery. The catheter tip has also been seen to impinge on the posterior wall during manipulation. Similar buckling of the catheter is often observed radioscopically during the actual recording of the wedge pressure. Either of these mechanisms or unusually prolonged contact may, in the case described, have initiated thrombosis in an atheromatous artery. The risk of pulmonary infarction following the wedge pressure technique is well recognized (Miller *et al.*, 1952; Houssey *et al.*, 1952) but this is peripheral in type and not due to thrombosis of a large pulmonary artery.

It is worth emphasizing that in our case the thrombosis was symptomless in life and but for the patient's post-operative death might have passed unrecognized. To prevent the occurrence of similar lesions it would be advisable, after insertion into the wedge position, to withdraw the catheter as far as possible without dislodging the tip. This manœuvre reduces buckling of the catheter and lessens the risk of trauma in the region of the pulmonary artery main stem. The time spent in the wedge position should be as short as possible.

Summary

An instance of thrombosis of the right main branch of the pulmonary artery following cardiac catheterization is described. Possible mechanisms of production are discussed.

We wish to thank Professor Crighton Bramwell and Professor A. C. P. Campbell for help in the preparation of this paper.

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ABSTRACTS OF CARDIOLOGY

Edited in collaboration with Abstracts of World Medicine

The Effects of Peripheral Arterial Embolism. R. L. RICHARDS. *Quart. J. Med.*, **23**, 73–90, Jan., 1954. 2 figs., 35 refs.

This review of the effect of embolism of the peripheral arteries is based on a survey of the literature and on personal observation in 52 cases (56 episodes of peripheral arterial embolism). Of the 52 patients, 15 recovered completely and 20 died; the remaining 17 had post-embolic ischæmia. Treatment included embolectomy in 19 cases and amputation of a limb in 4; the remaining cases were treated conservatively. The author states that he has seen only 4 cases " in which, without embolectomy, recovery of function in the limb was complete within 72 hours of the occurrence of the first symptom," the upper limb being affected in all four cases.

As regards the clinical features, a sudden transient pain may be felt in the limb at the site of the embolism. This pain arises from stimulation of the nerve endings in the arterial wall, the stimulus being associated with distension rather than spasm. The principal pain is due to ischæmia of the tissues; it develops gradually and is maximal on the distal side of the occlusion. Either numbness or coldness of the limb precedes pain in approximately one-third of all cases. The degree of paralysis varies considerably. The late effects of paralysis are often troublesome and are occasionally followed by permanent disability.

It is concluded that medical treatment should be instituted if the patient is seen within 8 hours of the onset of symptoms. Embolectomy is advised, however, if no improvement is observed after 2 to 3 hours.

A. Garland

Clinical Appraisal of Intra-arterial Priscoline Therapy in the Management of Peripheral Arterial Diseases. A. G. PRANDONI and M. MOSER. *Circulation* (*N.Y.*), **9**, 73–81, Jan., 1954.

The intra-arterial use of vasodilators might be expected to avoid some of the undesirable systemic effects of intravenous autonomic blocking agents. The injection into the femoral, radial, or brachial artery of " priscoline " (benzazoline; 2-benzyl-4:5 imidazoline hydrochloride), which has an adrenergic blocking and direct vasodilator action and is neither necrotizing to tissue nor irritant to the vascular endothelium, was therefore tried by the authors in the treatment of 250 patients with peripheral vascular disease.

The results were fairly satisfactory. Of 7 cases of Raynaud's disease improvement with healing of ulcers in 5 resulted, even when previous sympathectomy had been unsuccessful. In the treatment of 65 patients with arteriosclerosis obliterans the best results were obtained in those with ischæmic rest pain, but increased exercise tolerance was obtained in only a few. Skin temperature was raised in all but 21 cases, while in 9 cases a fall was observed. Of a group consisting of 50 men and one women with thrombo-angiitis obliterans, all had previously received various forms of treatment, including benzazoline by mouth, without success. Gangrene was present in 26 cases. Of the 51 patients, 14 obtained complete and 10 partial relief, improvement being greater in those who had given up smoking. Only 3 in the whole group required subsequent amputation. Exercise tolerance, however, was but rarely increased.

The authors conclude that although hexamethonium and " dibenzyline " frequently give better results, benzazoline by intra-arterial injection has a place where a possible reduction in blood pressure is undesirable, but that " uniformly good results should not be expected."

F. Starer

Problems in the Diagnosis and Surgical Treatment of Pulmonic Stenosis with Intact Ventricular Septum. J. W. KIRKLIN, D. C. CONNOLLY, F. H. ELLIS, H. B. BURCHELL, J. E. EDWARDS, and E. H. WOOD. *Circulation* (*N.Y.*), **8**, 849–863, Dec., 1953.

The authors discuss the pathological anatomy of the pulmonary outflow tract in cases of pulmonary stenosis without interventricular septal defect and describe the results of operation in 12 cases. There was marked hypertrophy of the muscle of the right ventricle which, in 4 of the 6 hearts examined, was sufficient to cause significant narrowing of the outflow tract.

It was found that although the right ventricular pressure fell sharply after dilatation, it might not reach a normal level for some months. The pressure fell most markedly in cases of pure valvular stenosis, but also fell considerably where a combined stenosis was encountered. It is suggested that a continued fall in pressure after valvotomy in the presence of infundibular stenosis may well be due to diminution in the hypertrophy of the right ventricular muscle, which is, at least in part, responsible for the infundibular stenosis.

The authors operate on asymptomatic patients only when the right ventricular pressure exceeds 75 mm. Hg. Of the 12 patients, 2 died as a result of the operation.

J. R. Belcher

Myocardial Infarction and its Treatment with Anticoagulants. Summary of Findings in 1,031 Cases. I. S. WRIGHT, D. F. BECK, and C. D. MARPLE. *Lancet*, **1**, 92–95, Jan. 9, 1954.

In 1946 the American Heart Association set up a committee to determine the value of anticoagulants in the treatment of myocardial infarction, a preliminary report, based on the first 800 cases, being published in 1948 (*Amer. Heart J.* **36**, 801). In the present paper the authors summarize the findings in a total of 1031 cases treated at 16 different centres in the U.S. over a period of 2 years.

Dicoumarol was given to 589 patients and the results of this treatment were compared with those obtained in 442 patients receiving "conventional" therapy only. The more important findings were as follows. Of the 442 patients in the control group 23% died within 6 weeks compared with 16% of the treated group. During the period of effective anticoagulant therapy—that is, from the fourth day of treatment to 4 days after the last dose of dicoumarol—9·5% of the treated patients died, whereas 17% of the untreated patients died during the corresponding period. During a 6-week observation period thrombo-embolic complications developed in 26% of the control group but in only 11% of the treated group. It is concluded that to confine anticoagulant therapy in myocardial infarction to the more seriously ill patients is not justified. *Bernard Isaacs*

Respiratory and Circulatory Studies of Patients with Mitral Stenosis. P. C. CURTI, G. COHEN, B. CASTLEMAN, J. G. SCANNELL, A. L. FRIEDLICH, and G. S. MYERS. *Circulation* (*N.Y.*), **8**, 893–904, Dec., 1953.

At the Massachusetts General Hospital, 16 patients with mitral stenosis were investigated before operation by means of cardiac catheterization and ventilatory and respiratory tests. The patients deemed to have the most severe mitral stenosis were found to have the highest pulmonary arterial resistance and the lowest resting cardiac output. Most of the patients showed a reduced vital capacity and a decreased maximum breathing capacity. The oxygen diffusing capacity was reduced in proportion to the severity of the disease and this finding was corroborated by lung biopsy, which showed thickening and fibrosis of the alveolar walls, a condition likely to hinder adequate oxygen diffusion. The degree of the pulmonary arterial and arteriolar changes found in lung-biopsy specimens, however, was not correlated with the calculated pulmonary arteriolar resistances. *James W. Brown*

Tricuspid Insufficiency. Observations Based on Angiocardiography and Cardiac Catheterization in Twelve Patients. C. T. DOTTER, D. S. LUKAS, and I. STEINBERG. *Amer. J. Roentgenol.*, **70**, 786–792, Nov., 1953.

Angiocardiography and cardiac catheterization were carried out in 12 cases of tricuspid insufficiency and in this paper the findings are discussed. All the patients had chronic rheumatic mitral stenosis and auricular fibrillation.

Cardiac catheterization is the most accurate diagnostic method, the diagnosis being established by this means in all 12 cases. A significant feature of the pressure curve was a high plateau in tracings from the right atrium.

The authors do not consider that the presence of tricuspid insufficiency contraindicates operation on the mitral valve. *Sydney J. Hinds*

Surgical Closure of Atrial Septal Defects. R. E. GROSS and E. WATKINS. *Arch. Surg.* (*Chicago*), **67**, 670–685, Nov., 1953.

The authors, writing from Harvard Medical School, review the various surgical techniques now employed in the treatment of atrial septal defects. They state that in principle these fall into four main groups. (1) Repair under direct vision, employing some form of artificial circulation or refrigeration and temporary arrest of the circulation. (2) Suture of the auricular wall itself to the margin of the defect. (3) "Blind" suture of the anterior edge of the defect to the posterior auricular wall. (4) Suture of some inert material such as polyethylene directly to the edges of the defect, using the principle of the atrial wall as described by the authors (*New Engl. J. Med.*, 1952, **247**, 455).

In the authors' experience Method 3 is ideal for high posterior and small defects and Method 4 is the best for larger and anterior lesions, but as yet no completely adequate method has been devised to deal with the large, low, anterior defects which have no edges and which abut on the tricuspid valve. They mention the not uncommon association of anomalous pulmonary venous drainage with atrial septal defects, and stress the importance of the correction of this lesion. Of 12 of the authors' patients treated by Methods 3 and 4, 5 died as a result of the operation, but all 7 survivors had considerable subjective improvement and 3 out of 4 of these who were examined by cardiac catheterization after operation showed no evidence of any interatrial shunt.

J. R. Belcher

Aortic Stenosis. Diagnosis and Treatment. A. LOGAN and R. TURNER. *Lancet*, **1**, 1091–1095, May 29, 1954.

In reporting 9 cases of aortic stenosis treated by aortic valvotomy at the Western General Hospital, Edinburgh, the authors review the symptoms and clinical signs of the disease. They suggest that the diagnosis in such cases is often missed because even severe stenosis may exist in the absence of some of the classic signs.

The operation consisted in dilatation of the aortic valve, approached by the ventricular route, by means of a mechanical dilator similar in type to the Brock pulmonary dilator but larger in size, the blades being 10 cm. long and the maximum spread 4 cm. Of the 9 patients operated on, 4 had associated mitral disease, and in these the two valvotomies were performed at the same thoracotomy, the aortic valve being dealt with before the mitral valve.

Only one of the 9 patients died as a result of the operation, the condition of all the rest being improved.

J. R. Belcher

Assisted Circulation by Pump-oxygenator during Operative Dilatation of the Aortic Valve in Man. I. AIRD, D. G. MELROSE, W. P. CLELAND, and R. B. LYNN. *Brit. med. J.*, **1**, 1284–1287, June 5, 1954.

The authors briefly discuss the clinical application of extracorporeal circulation by means of an artificial heart-lung machine. One of the main risks of cardiac surgery is the danger of inadequate coronary flow, which may result in the development of ventricular fibrillation. An apparatus, consisting essentially of a pump-oxygenator, has been devised and described by Melrose *et al.* (*Brit. med. J.*, 1953, **2**, 57) whereby the circulation may be assisted and which may therefore prevent the onset of fibrillation by maintaining an efficient coronary circulation.

In the present paper a full description is given of a case of mitral incompetence with aortic stenosis in which this apparatus was used and double cardiotomy successfully performed. Blood was removed from the inferior vena cava by a catheter inserted in the saphenous vein, passed through the machine, and then returned to the aorta by way of a catheter in the superficial femoral artery. The operation lasted for some 2½ hours, during which the patient lost 6 pints (3·4 litres) of blood, for which a transfusion of 7½ pints (4·3 litres) was given. The flow of blood in the machine varied from 500 to 800 ml. per minute, and it was estimated that in all some 70 litres of blood passed through the pump–oxygenator, or about 30 per cent of the total cardiac output. Recovery was uneventful apart from some cyanosis, which passed off within 4 hours, and thrombophlebitis of the catheterized saphenous vein, and the patient's condition has been greatly ameliorated. *J. R. Belcher*

The Role of Intimal Hæmorrhage in Coronary Occlusion. R. A. B. DRURY. *J. Path. Bact.*, **67**, 207–215, Jan., 1954.

In this study 55 hearts from subjects dying from coronary arterial disease were examined, together with a control group. Intimal hæmorrhage was frequently found in the coronary arteries, and nearly always resulted from hæmorrhage into an atheromatous plaque, the overlying endothelium of which had given way. Thrombosis was also found to be associated with rupture of the endothelium over an atheromatous plaque, but was not related to intimal hæmorrhage. No evidence was found to support Wartman's view that massive intimal hæmorrhage may sometimes cause sudden coronary arterial occlusion. The author believes that although intimal hæmorrhage is a common finding in cases of coronary thrombosis, it is one of little importance and should in no way be regarded as a contraindication to anticoagulant therapy. *G. J. Cunningham*

The Treatment of Shock Associated with Myocardial Infarction. G. C. GRIFFITH, W. B. WALLACE, B. COCHRAN, W. E. NERLICH, and W. G. FRASER. *Circulation (N.Y.)*, **9**, 527–532, April, 1954.

For the purposes of this investigation of the effect of the shock which is associated with myocardial infarction, a systolic blood-pressure reading of 80 mm. Hg or below in previously normotensive patients, or of 100 mm. Hg or below in formerly hypertensive patients, was accepted as evidence of shock, provided the hypotension lasted for an hour or more and was accompanied by signs of peripheral circulatory collapse. Examination of the records of 816 cases of myocardial infarction admitted during 18 months in 1949–51 showed that of these patients 161 (20%) had evidence of shock as defined and 128 of these died, a mortality of 81 per cent.

The later group now described consisted of 134 patients with shock due to recent myocardial infarction who were admitted to the hospital during 18 months in 1951–2. The importance of early treatment of shock is emphasized by the fact that of the 60 patients treated within three hours of onset only 8 died, a mortality of 13 per cent, compared with 56 (76%) of the 74 patients treated after three hours; the over-all mortality in the whole group was 48 per cent.

If routine treatment did not control shock, one or more of the following additional measures were employed. Intravenous infusion (9 cases, control of shock in 2); retrograde arterial infusion of plasma or blood into the radial artery (19 cases, shock controlled in 12); administration of noradrenaline by intravenous drip using a solution of 8 mg. in 1 litre of 5 per cent glucose in water (30 cases, shock controlled in 17); methoxamine, given either intramuscularly in a dose of 20 mg., or 5 mg. slowly intravenously and repeated as necessary (49 cases, shock controlled in 10, no pressor effect obtained in 35); *iso*propylnoradrenaline, 2 to 3 mg. slowly intravenously, followed by 7·5 or 15 mg. sublingually as required after shock had been overcome, given at intervals of 15 or 30 minutes (26 patients, shock controlled in 7, no pressor effect in 16). *A. Schott*

Endomyocardial Fibrosis. J. D. BALL, A. W. WILLIAMS, and J. N. P. DAVIES. *Lancet*, **1**, 1049–1054, May 22, 1954.

Endomyocardial fibrosis is a common cause of heart failure in Uganda. The authors have observed it only in Africans, in whom it occurs at all ages and with equal sex incidence, and they here report 20 cases studied clinically during the period 1950–3, in all of which post-mortem proof of diagnosis was obtained. The morbid anatomical features of this condition are: normal pericardium and epicardial muscle; endocardial fibrosis in patches or involving nearly the whole of one or both ventricles, several millimetres thick, and pearly white in appearance when not concealed by thrombus; fibrosis extending up to two-thirds of the way into the myocardium; fibrosis of the papillary muscles, thickening and shortening of the chordæ, and resultant incompetence of the mitral and tricuspid valves; and normal coronary arteries and aortic and pulmonary valves. Rarely, bacterial endocarditis is found.

Of the 20 patients, 14 presented with heart failure and signs of incompetence of auriculo-ventricular valves (10 mitral only, 2 tricuspid only, and 2 both mitral and tricuspid); 4 had signs and symptoms of right and left heart failure without other distinguishing features; and the remaining 2 had severe endocardial fibrosis of the

right ventricle with almost complete obliteration of the inflow tract and some tricuspid incompetence—producing a clinical picture and hæmodynamic upset not unlike that of constrictive pericarditis. One of these last two patients had a very large hydropericardium. The longest period of symptoms was 7 years and the longest period of observation 20 months. No treatment was beneficial.

K. G. Lowe

Coarctation of the Pulmonary Artery. T. SØNDERGAARD. *Dan. med. Bull.*, **1**, 46–48, April, 1954.

The author describes 3 cases of cyanotic congenital heart disease in which at operation the pulmonary artery was found to be constricted at its bifurcation. This condition, for which the term "coarctation of the pulmonary artery" is suggested, does not seem to have been previously suspected. In all 3 cases the constriction involved the first part of each branch of the pulmonary artery, and fibrous bands from the ligamentum arteriosum appeared to take part in the constriction.

The author states that coarctation of the pulmonary artery is more serious than that of the aorta, because in the former it is not possible to establish a collateral circulation as in the case of the aorta.

G. S. Crockett

Further Observations on the Closure of Atrial Septal Defects. H. B. SHUMACKER, H. KING, and P. R. LURIE. *Circulation* (*N. Y.*), **9**, 504–510, April, 1954.

In an earlier paper (*Amer. Surg.*, 1953, **138**, 404) a new technique for closure of an atrial septal defect was described in which a half-moon-shaped pocket of pericardium was sutured to an incision in the atrial wall, this pocket being then invaginated into the atrial cavity so that its posterior wall could be sutured to the wall of the septal defect. This procedure, although satisfactory in dogs, was not successful in two patients, one of whom died 5 months after operation; at necropsy it was found that the graft had completely disappeared, this being attributed to failure of revascularization of the pericardium. In the present paper the authors describe a modification of this method in which thin, finely-woven nylon fabric was used instead of pericardium. By this technique a large septal defect which had been produced experimentally in 13 dogs was closed. The animals were killed 11 to 189 days after operation and necropsy showed complete closure in 12; in the remaining animal there was a defect 1 mm. in diameter. In 2 dogs the graft was not covered by endothelium 11 and 19 days respectively after operation. No gross thrombi were visible in the atrium or on the graft, and in no instance was there obstruction to the venæ vacæ or coronary sinus.

This operation was performed with success on a boy aged 11 years with an atrial septal defect about 2 cm. in diameter and pulmonary stenosis. The septal defect was closed by invaginating the nylon pocket into the atrium and fixing it to the edge of the septal defect with four interrupted sutures of 4-0 silk and four continuous sutures of the same material between the interrupted sutures. A pulmonary valvotomy was also performed. The patient was well and free from symptoms 5 months after operation.

R. L. Hurt

The Role of Auscultation in the Diagnosis of Congenital Heart Disease. A Phonocardiographic Study of Children. J. D. L. REINHOLD and A. S. NADAS. *Amer. Heart J.*, **47**, 405–423, March, 1954.

The auscultatory signs of congenital heart disease were studied in 64 children aged 5 to 15 years. Particular attention was paid to phonocardiograms, which were recorded with stethoscopic and logarithmic microphones from the apex, second and fourth left intercostal spaces, and the second right intercostal space parasternally. A detailed description of the normal phonocardiogram is given, and the authors then recount their findings in cases of aortic stenosis, pulmonary valvular stenosis, ventricular and atrial septal defect, Fallot's tetralogy, and atypical patent ductus arteriosus. Illustrative phonocardiograms and composite diagrams showing the time-relations of the various features with those of the electrocardiogram, apex cardiogram, and carotid pulse tracing are presented, and reference is made to the intensity, distribution, and transmission of the sounds and murmurs described.

The study revealed several rather characteristic phonocardiographic appearances. Among the more valuable points of differential diagnosis was the degree of splitting of the second heart sound, which was greatest with atrial septal defects, normal (0·04 second or less) in cases of ventricular septal defect or patent ductus arteriosus, and negligible in pulmonary and aortic stenosis. In normal children, the second sound is louder on the left than on the right side in the second intercostal space. This relationship is preserved in the majority of cases of atrial septal defect, small ventricular septal defects, and patent ductus arteriosus, but is usually exaggerated in the presence of pulmonary hypertension and reversed in cases of pulmonary stenosis.

The authors state their belief that a search for these phenomena, and others which they describe, by auscultation and their occasional registration by phonocardiography may help in the differential diagnosis of congenital heart disease.

D. Goldman

Cessation of Circulation in General Hypothermia. III. Technics of Intracardiac Surgery under Direct Vision. H. SWAN and I. ZEAVIN. *Ann. Surg.*, **139**, 385–396, April, 1954.

In experimental animals occlusion of the inflow to the heart for the purposes of intracardiac surgery under direct vision can be maintained safely at normal temperatures for 1½ minutes, and with only slight risk up to 4 minutes. Thereafter the mortality rises sharply, death being due to ventricular fibrillation or cerebral changes.

The use of hypothermia during cardiac operations in man, as pioneered by Bigelow, enables the great veins to be occluded for periods up to 15 minutes, while the danger of ventricular fibrillation can be obviated to some extent by hyperventilation and infusion of potassium salts. The authors have operated on 16 patients under hypothermia, with 2 deaths. The process of cooling,

which is carried out under general anæsthesia in a bath of ice water at 2° to 4° C., may take anything from 15 minutes to 1¼ hours. It is noted that fat persons cool more slowly than thin. The operation is carried out when the temperature is between 23° and 26° C.

The major complication is ventricular fibrillation, for the treatment of which the authors have found little value in electrical defibrillation and prefer to perfuse the coronary arteries with potassium chloride solution (1 mEq. per litre) followed by cardiac massage, which is maintained as the patient is warmed. Some hearts recover as the temperature rises; the use of adrenaline is not recommended. *T. Holmes Sellors*

Heparin and Ethyl Biscoumacetate in Prevention of Experimental Venous Thrombosis. P. JEWELL, T. PILKINGTON, and B. ROBINSON. *Brit. med. J.*, **1**, 1013–1016, May 1, 1954.

The efficacy of heparin was compared with that of ethyl biscoumacetate in the prevention of thrombosis following experimentally induced phlebitis in rabbits. The sclerosing agent (0·1 ml. of monoethanolamine oleate) was injected into one of the marginal ear veins in the direction of the blood flow and held in a 4-cm. length of vein for 5 minutes. In this way, extensive thrombosis was produced. One group of 31 rabbits received ethyl bicoumacetate by mouth in 10- to 40-mg. doses twice daily for 3 days before the injection of the sclerosing agent. Administration of the anti-coagulant drug was continued for another 5 days, the animals then being killed. Only 4 rabbits in this group showed extensive thrombosis. A second group of 34 rabbits received heparin as follows: intravenous injection of 500 to 1000 units every 6 hours (11 animals); intramuscular injection of 1000 to 1500 units every 6 hours (10 animals); intramuscular injection of 500 to 1000 units every 4 hours (13 animals). Extensive thrombosis was found in 25 of the 34 veins tested, all three methods of heparin administration being equally unsuccessful in preventing thrombosis. It is considered that since the dosage of ethyl bicoumacetate was only slightly (two to three times) greater than that given to human beings, this difference between the efficacy of the two drugs is important.

[The authors' findings call for critical assessment of the value of these two drugs in the prevention of thrombosis in man.] *G. B. West*

The Incidence and Severity of Atherosclerosis in Estrogen-treated Males, and in Females with a Hypoestrogenic or a Hyperestrogenic State. A. U. RIVIN and S. P. DIMITROFF. *Circulation* (*N.Y.*), **9**, 533–539, April, 1954.

In order to explore the possibility that œstrogenic hormones may inhibit the development of atherosclerosis, a study was made of the necropsy records of male patients with carcinoma of the prostate who had been treated with œstrogens and of female patients with carcinoma of the breast—these two groups being considered to have been in a state of hyperœstrogenism—and of surgically castrated females, who had thus been in a state of hypo-œstrogenism.

In all, 153 cases of carcinoma of the prostate were studied. These were divided into cases treated with œstrogens for 3 months or more and control cases in which less than 3 months' œstrogen treatment or none at all had been given. The treated cases were further subdivided according to the dosage employed (30 cases in which a dose of 75 mg. of stilbœstrol or more had been given daily, which were compared with 27 controls, a significant difference in severity of atherosclerosis being found only in the coronary arteries. On the other hand the incidence of atherosclerosis in 39 cases of carcinoma of the breast was lower than that in a series of normal subjects reported by other workers while that in 99 female subjects who had undergone bilateral oophorectomy at least one year before death and before the age of 50 was significantly higher.

These results are held to support the theory that ovarian secretions protect against atherosclerosis, this accounting for the sex difference in incidence of the disease. *Peter Harvey*

Hypotensive Action of Reserpin. A. E. DOYLE and F. H. SMIRK. *Lancet*, **1**, 1096–1097, May 29, 1954.

To determine whether reserpine, an alkaloid of *Rauwolfia serpentina*, acts as a placebo or a sedative or has a hypotensive effect, large doses were given to 20 hypertensive patients. The dose of reserpine usually given is 0·75 to 1·5 mg. daily, but in this investigation it was decided to try the effect of 2 to 3 mg. by mouth three times a day. After these large doses the blood pressure usually fell significantly, more so than after a placebo, the trough occurring 5 hours after the dose. For example, the systolic pressure fell more than 40 mm. Hg in 16 patients and more than 60 mm. Hg in 12, while the diastolic pressure fell more than 25 mm. Hg in 17 patients and more than 45 mm. Hg in 7. The fall in blood pressure began on the first or second day of treatment and often persisted for 24 hours after treatment ceased. There were, however, unpleasant side-effects with these large doses, including flushing, conjunctival injection, nasal blockage, fatigue and sleepiness, depression, shivering, restlessness, and a sensation of heat. *Arthur Wilcox*

An Atlas of Congenital Anomalies of the Heart and Great Vessels. JESSE E. EDWARDS, THOMAS J. DRY, ROBERT L. PARKER, HOWARD B. BURCHELL, EARL H. WOOD and ARTHUR H. BULBULIAN. Oxford: Blackwells Scientific Publications, 1954. Pp. 202, Figs. 256. 97*s*.

This atlas, compiled by members of the Mayo Clinic and Mayo Foundation, is in effect a new work although it includes the material contained in the earlier atlas published in 1948. There are numerous additions to the list of malformations discussed and in many instances the results of studies by cardiac catheterization, oximetry, and dye dilution methods are presented. The illustrations are well reproduced and there are numerous colour photographs of models of specimens. The text, which is brief, includes in summary form the important clinical features of the various anomalies described and there is an excellent bibliography. This book is a valuable addition to the literature on congenital heart disease and can be thoroughly recommended. *G. W. Hayward*

PATENT DUCTUS ARTERIOSUS WITH PULMONARY HYPERTENSION

BY

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Several patients with severe pulmonary hypertension associated with patent ductus arteriosus have been described in the past few years by Johnson *et al.* (1950), Campbell and Hudson (1951), Bothwell *et al.* (1952), Dammann and Sell (1952), Cosh (1953), Hultgren *et al.* (1953), and Smith (1954), and these reports suggest that pulmonary hypertension may be a primary abnormality and not secondary to an increased pulmonary blood flow from a shunt through the patent ductus arteriosus. The view, that severe pulmonary hypertension is not a direct complication of patent ductus arteriosus, receives some support from Brown's (1950) observation that cyanosis does not usually occur in the natural history of the lesion, while experience of patients with patent ductus arteriosus associated with severe pulmonary hypertension suggests that it is justifiable to regard this combination as a specific entity, which must be considered in the differential diagnosis of any patient presenting signs of pulmonary hypertension, irrespective of other auscultatory signs or the presence or absence of cyanosis.

The features of eight patients with severe pulmonary hypertension and patent ductus arteriosus are described below and an account of the pathological findings is given in two who died. The clinical manifestations of this combination are defined and its diagnosis by cardiac catheterization and angiocardiography is discussed.

Clinical Features

Symptomatology. All eight patients complained of breathlessness on exertion and had frequent coughs and colds. Cases 2 and 5 had a history of hæmoptysis and Case 5 eventually died following a rupture of the pulmonary artery. Four of the five adult patients noted that they were occasionally bluer than normal. Case 2 complained of palpitation.

Signs. From the classical signs of pulmonary hypertension such as a giant "*a*" wave in the jugular venous pulse, a systolic lift over the right ventricular outflow tract, a palpable second pulmonary sound, and an abnormally loud pulmonary element of the second heart sound on auscultation, it was possible to make a clinical diagnosis of pulmonary hypertension in all eight patients. The other clinical features are shown in Table I.

Electrocardiography. The cardiogram showed right ventricular dominance in all patients and there was also evidence of right bundle branch block in Cases 1 and 6 (Fig. 1 and 2).

Radiological Examination. The postero-anterior teleradiograms of the present group of patients

* Leverhulme Research Scholar, Royal College of Physicians.

are reproduced in Fig. 3 and 4. Right ventricular hypertrophy was present in all of them and the other radiological findings are summarized in Table II.

Angiocardiography was performed in six of the eight cases. Films taken two to three seconds after the injection of the contrast medium showed simultaneous filling of the pulmonary arteries and descending aorta, with no dye in the ascending aorta, in Cases 1, 3, 6, 7, and 8 (Fig. 5). In Case 2, early filling of the ascending aorta and pulmonary arteries from the right ventricle showed

TABLE I

FEATURES OF EIGHT PATIENTS WITH PATENT DUCTUS ARTERIOSUS ASSOCIATED WITH SEVERE PULMONARY HYPERTENSION

Case	Age	Sex	Systemic blood pressure in arms (mm. Hg)	Cyanosis	Finger clubbing	Auscultatory signs in pulmonary area	Other auscultatory signs	Hb grams per 100 ml.	Hæmatocrit	Associated lesions
1	5	F	170/80	Lower extremities only	Present	Gibson murmur. P2 loud and split	Diastolic murmur and systolic murmur at apex	14·4	—	Coarctation of aorta
2	26	F	115/75	Slight	Present	No murmur. P2 loud and split	Nil	18·1	58	Overriding aorta
3	6	M	105/35	Absent	Absent	Systolic murmur. P2 loud and split	Diastolic and systolic murmur at apex	12·2	40	Ventricular septal defect
4	58	F	160/105	Moderate	Absent	No murmur. P2 loud and split	Triple rhythm at lower end of sternum	25·0	77	Nil
5	22	F	190/90	Moderate	Present	Diastolic murmur. P2 loud and split	Diastolic murmur at apex	20·0	71	Mitral stenosis
6	46	F	100/60	Absent	Absent	No murmur. P2 loud and split	Rumbling diastolic murmur at apex	14·8	45	Nil
7	8	F	90/?	Lower extremities only	Absent	Systolic and diastolic murmurs. P2 loud	Nil	11·1	—	Nil
8	34	F	100/70	Moderate	Present	Systolic murmur. P2 loud and split	Nil	14·5	—	Nil

that an overriding aorta was present. This patient was, however, shown by cardiac catheterization to have, in addition, a patent ductus arteriosus and the catheter was passed from the pulmonary artery into the descending aorta (Fig. 6).

Cardiac Catheterization. This investigation was carried out in all patients except Cases 4 and 5, and in five of the six, the catheter was passed through the ductus (Fig. 6 and 7). The other findings at cardiac catheterization are summarized in Table III.

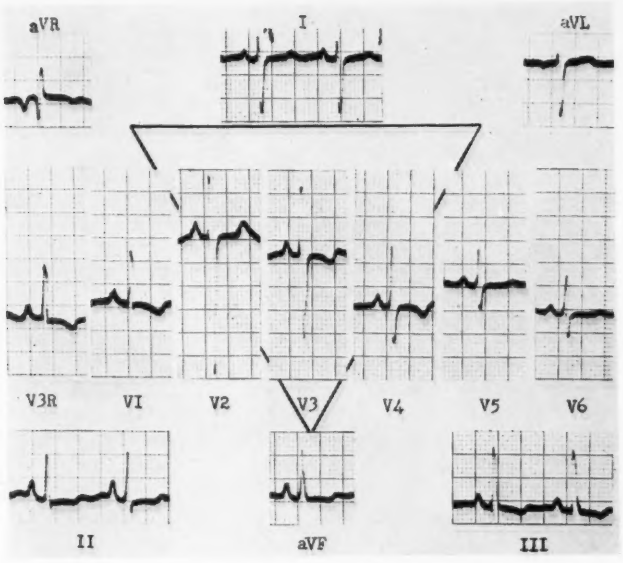

FIG. 1.—Case 2. Electrocardiogram showing pattern of right ventricular hypertrophy and clockwise rotation of a vertical heart.

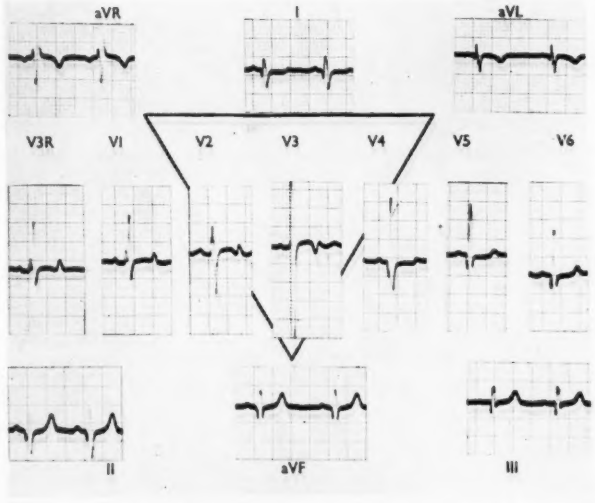

FIG 2.—Case 1. Electrocardiogram showing pattern of incomplete right bundle branch block.

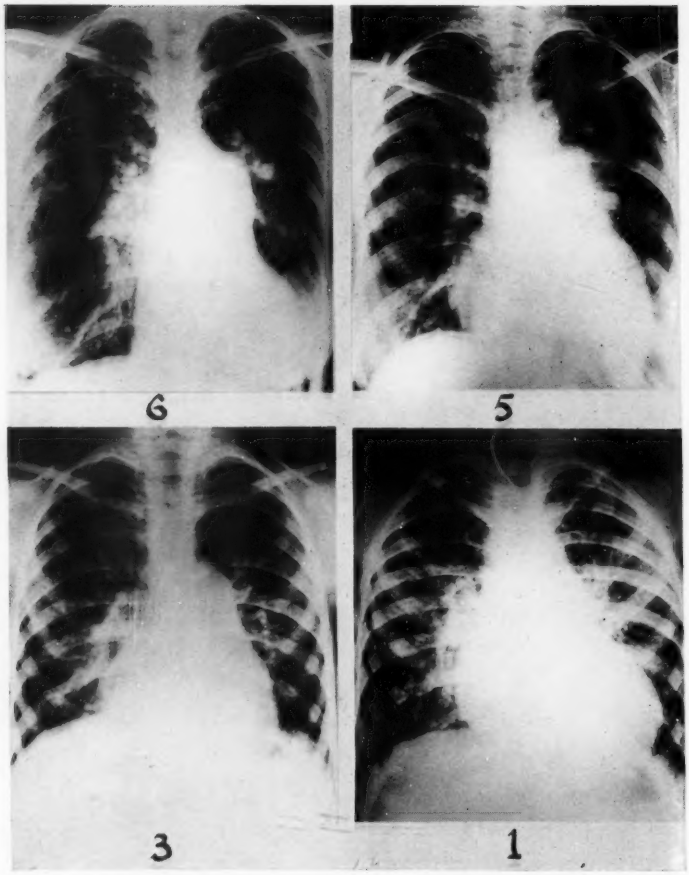

FIG. 3.—Postero-anterior teleradiogram of four patients (Cases 6, 5, 3, and 1) with patent ductus arteriosus and pulmonary hypertension.

TABLE II

ABNORMAL RADIOLOGICAL FINDINGS IN EIGHT PATIENTS WITH PATENT DUCTUS ARTERIOSUS AND SEVERE PULMONARY HYPERTENSION

Case	Degree of cardiac enlargement	Prominence of main pulmonary artery	Abnormal pulsation of the pulmonary artery	Left atrial enlargement
1	Marked	Moderate	Present	Present
2	None	Slight	Absent	Absent
3	Moderate	Marked	Present	Absent
4	Slight	Slight	No note	Absent
5	Moderate	Extreme	Present	Absent
6	Slight	Marked	Present	Absent
7	Slight	Slight	Present	Absent
8	Slight	Moderate	Present	Absent

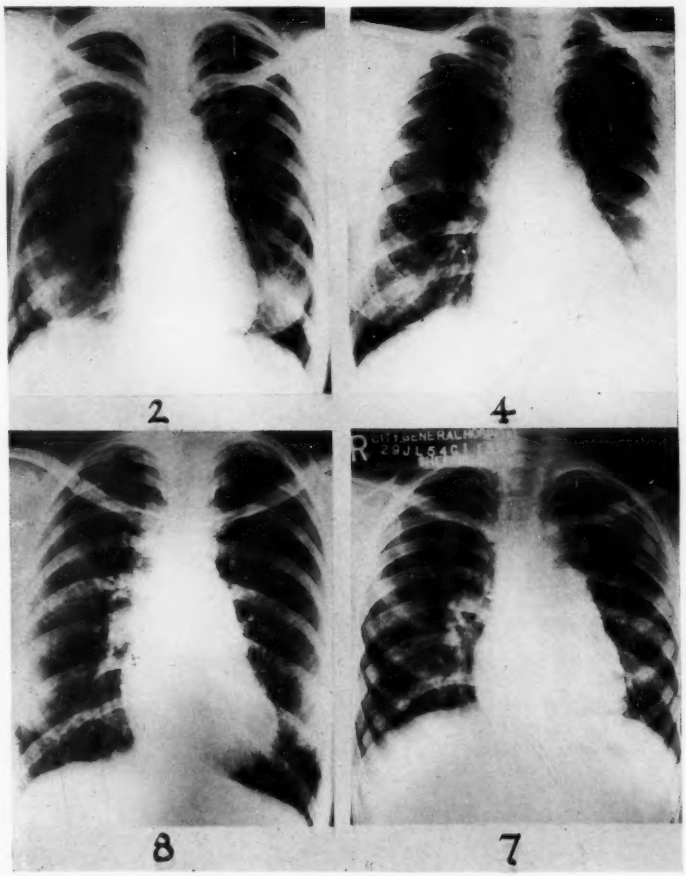

FIG. 4.—Postero-anterior teleradiogram of four patients (Cases 2, 4, 8, and 7) with patent ductus arteriosus and pulmonary hypertension.

AUTOPSY FINDINGS

Case 4. The heart weighed 460 g. and the right ventricle was dilated and hypertrophied. The wall of the right ventricle was 1·6 cm. thick and that of the left ventricle 1·8 cm. The main pulmonary artery was dilated and the abnormally dilated and thick-walled intrapulmonary arteries stood out more clearly than usual on the cut surface of the lung. The left pulmonary artery was blocked by ante-mortem thrombus and old portions of ante-mortem thrombus were found in its branches, especially those to the lower lobe which was infarcted and showed pleurisy of several days' duration. There was a large patent ductus arteriosus leading from the descending aorta into the pulmonary artery at its bifurcation. This vessel was about 1 cm. long and about 2 cm. in diameter and its site of origin in the descending aorta showed that it was a patent ductus arteriosus rather than an aorto-pulmonary septal defect. There was widespread atheroma of both extrapulmonary and the elastic intrapulmonary arteries (Fig. 8 and 9). There was no evidence of mitral stenosis or a septal defect.

On histological examination the elastic pulmonary arteries (>1 mm. in diameter) showed gross atheromatous change in the intima. In some of these vessels the atheromatous material was four times the

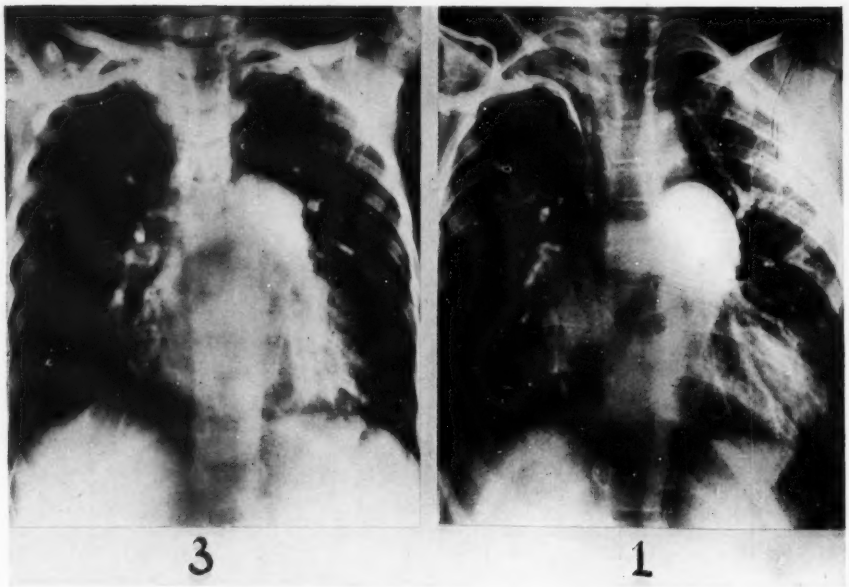

FIG. 5.—Antero-posterior angiocardiograms taken 3 seconds after the injection of the contrast medium in Cases 1 and 3, showing simultaneous filling of the pulmonary arteries and the descending aorta.

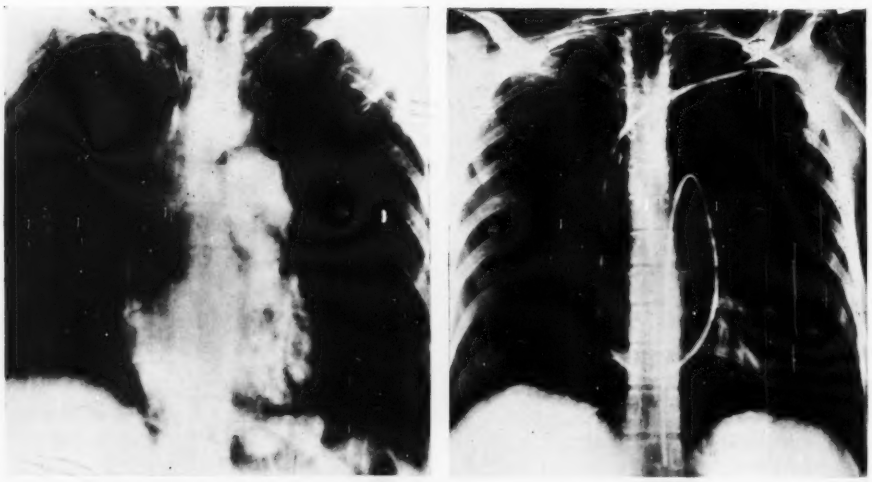

FIG. 6.—Case 2. The antero-posterior angiocardiogram, reproduced on the left, shows simultaneous filling of the pulmonary arteries and the ascending aorta from the right ventricle 3 seconds after the injection of the contrast medium. The film on the right shows a cardiac catheter passing from the pulmonary artery through a patent ductus arteriosus into the descending aorta in the same patient.

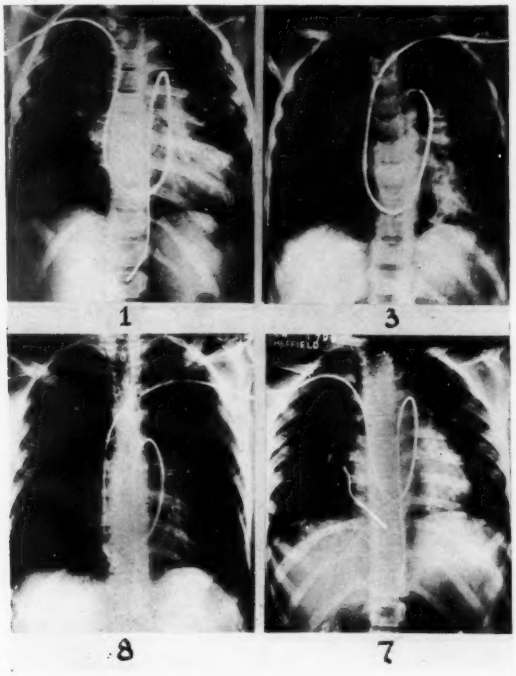

FIG. 7.—Films taken at cardiac catheterization in Cases 1, 3, 7, and 8, showing the cardiac catheter passing from the pulmonary artery through the patent ductus into the descending aorta. In Case 3 the descending aorta has been outlined by the injection of contrast medium through the catheter.

TABLE III

RESULTS OF CARDIAC CATHETERIZATION IN SIX PATIENTS WITH PATENT DUCTUS ARTERIOSUS AND SEVERE PULMONARY HYPERTENSION

Case	Blood oxygen saturation, percentages						Pulmonary artery blood pressure (mm. Hg)	Aortic blood pressure (mm. Hg)
	Femoral artery	Inferior vena cava	Superior vena cava	Right auricle	Right ventricle	Pulmonary artery		
1	97	—	—	77	78	78	120/100	105/95
2	86	71	70	71	71	75	125/75	130/75
3	Aortic 98 *83	67	69	69	Low 74 High 83	86	105/60	115/70
6	97	85	71	79	77	87	100/55	Not recorded
7	92	70	72	62	65	67	120/80	110/70
8	80	54	53	53	55	63		

* While under general anæsthesia for angiocardiogram.

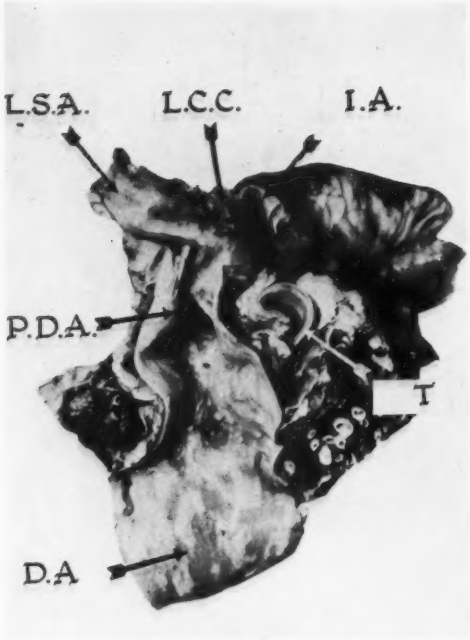

FIG. 8.—The aorta has been opened from behind to show the opening of the large patent ductus arteriosus beyond the origin of the left subclavian artery. The hypertrophied pulmonary vessels are obvious in the cut section of the lung. The aorta shows atheromatous change. Case 4.
T=Trachea. DA=Descending Aorta. PDA=Patent Ductus Arteriosus. LSA=Left Subclavian Artery. LCC=Left Common Carotid Artery. IA=Innominate Artery.

FIG. 9.—The heart and great vessels have been dissected to show the patent ductus arteriosus passing from the bifurcation of the pulmonary artery into the descending aorta. The right ventricle is hypertrophied and there is atheroma in the patent ductus and the aorta. Case 4.
A=Aorta. PDA=Patent Ductus Arteriosus. LPA=Left Pulmonary Artery. RPA=Right Pulmonary Artery. LL=Left Lung. RV=Right Ventricle.

thickness of the media. At the junction of the media and intima the elastic fibres were ruptured in many places, but the more peripheral fibres were normal. The adventitia was normal (Fig. 10).

The muscular arteries (0·1–1 mm. in diameter) showed a proliferation of fibro-elastic tissue in the intima. The lumen of most of the vessels was narrowed, while in others it was completely blocked; recanalization had occurred in some vessels. The media of the small muscular arteries was hypertrophied. Both elastic membranes were well defined and, although the internal elastic membrane was thicker than normal, it was not split. The adventitia was normal (Fig. 11). The arterioles (<0·1 mm. in diameter) showed the same changes in the intima and media as the muscular arteries and many of these vessels were completely blocked. In some, the proliferated intimal tissue had completely disorganized the structure of the vessels (Fig. 12). The pulmonary veins were normal and there was no evidence of thrombosis in the small veins.

Case 5. There was a hæmopericardium from a rupture of a dissecting aneurysm of the pulmonary artery and 520 ml. of blood clot were present in the pericardial cavity. The heart was enlarged and weighed 520 g. The right ventricle was dilated and hypertrophied and its wall was 1·5 cm. thick. The main pulmonary artery was dilated. The pulmonary artery and aorta were both very friable and the aorta was two-thirds the average diameter for a person of this height and weight. The aorta was collapsed like a flat ribbon and tore like wet blotting paper. There was a hæmatoma in the wall of the pulmonary artery above the pulmonary valve and bleeding from this had given rise to the hæmopericardium. The blood had spread between the media and adventitia. The dissected wall extended 5 cm. above the valve and the site of rupture was 1·5 cm. above the valve on the anterior surface. The length of the rupture was 0·8 cm. There was an

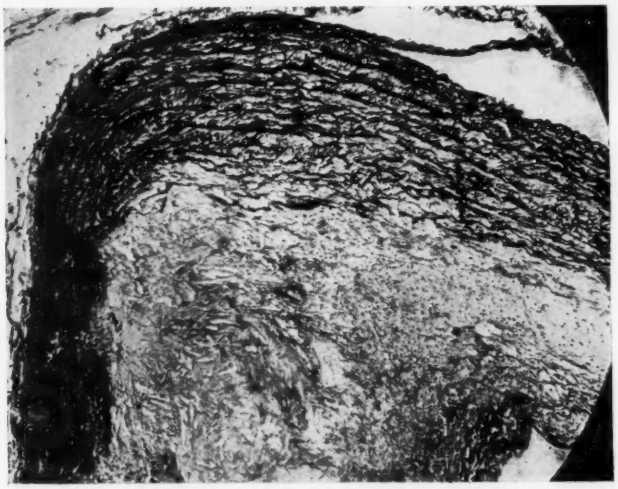

FIG. 10.—Transverse section of elastic pulmonary artery, showing gross atheromatous change in the intima. The elastic fibres are ruptured in many places at the junction of media and intima. Veerhoff/Van Gieson, ×52. Case 4.

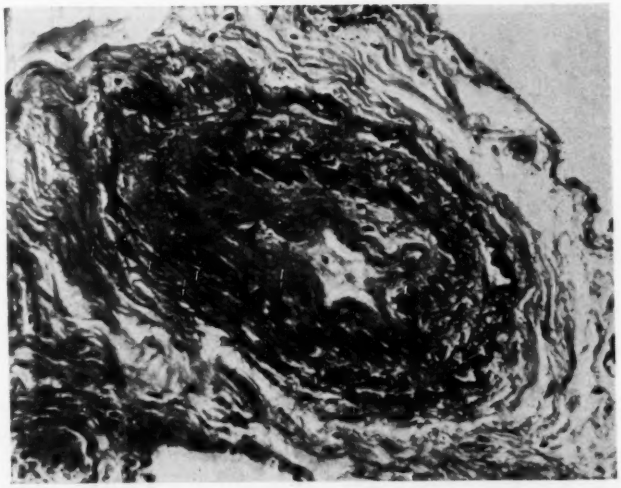

FIG. 11.—Transverse section of muscular pulmonary artery. There is proliferation of fibroelastic tissue in the intima. The media is hypertrophied and both elastic laminæ are thick. Veerhoff/Van Gieson, ×200. Case 4.

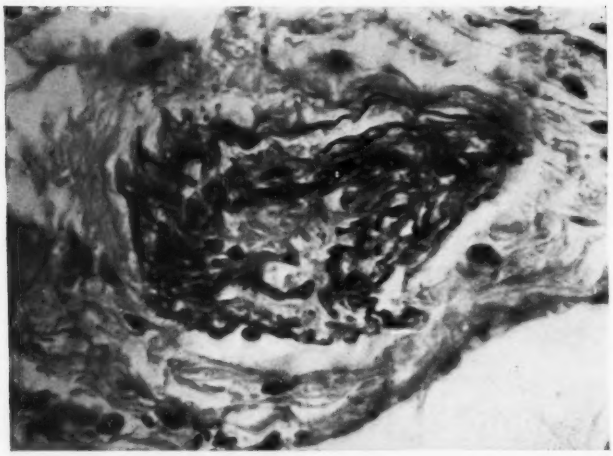

FIG. 12.—Transverse section of pulmonary arteriole. There is proliferation of intimal fibrous tissue, obliterating the lumen. The media is hypertrophied. Veerhoff/Van Gieson, ×530. Case 4.

FIG. 13.—Part of transverse section of main pulmonary artery, showing areas of medionecrosis. Case 5.

abnormal communication, of no appreciable length, 1·5 cm. in diameter, which opened into the aorta 2 cm. below the lumen of the left subclavian artery (Fig. 14) and into the left pulmonary artery at its origin 4·5 cm. above the pulmonary cusps. The site of the opening of this abnormal communication into the aorta suggested it was a patent ductus arteriosus rather than an aorto-pulmonary septal defect. There was an isolated plaque of atheroma in the ductus itself but the rest of the pulmonary arteries were free. A narrowed mitral ring admitted the tip of one finger with difficulty. The tricuspid valve admitted only two fingers. There was no evidence of a septal defect. The aortic valve had two cusps and there was thickening and slight calcification at the expected site of the missing commissure of the fused cusp. The papillary muscles

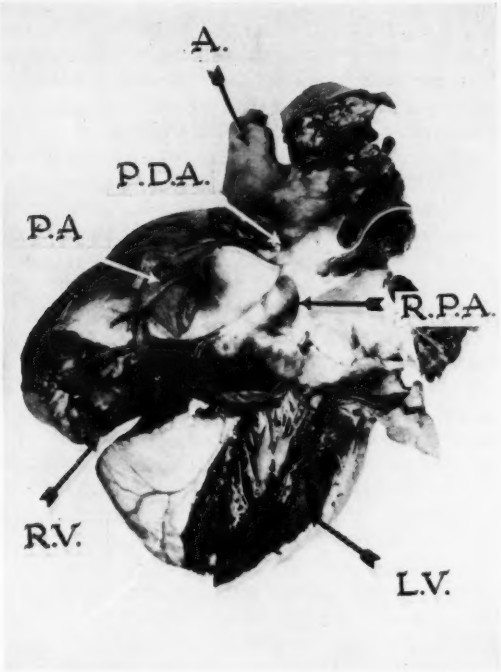

FIG. 14.—The heart and great vessels, showing a window-like patent ductus arteriosus, which has been opened, passing from the origin of the left pulmonary artery into the descending aorta. The wall of the main pulmonary artery is split and this contained blood clot. The right ventricle is thicker than the left. The aorta is free from atheroma. Case 5.
A=Aorta. PDA=Patent Ductus Arteriosus. RPA=Right Pulmonary Artery. PA=Pulmonary Artery. LV=Left Ventricle. RV=Right Ventricle.

in the right ventricle were twice as thick as in the left. The coronary arteries were normal. The main pulmonary artery and aorta on histological examination showed the changes of medio-necrosis. There were bluish hyaline streaks which stained metachromatically as pseudo-mucin and, in addition, some elastic fibres stained irregularly (Fig. 13). These changes were extensive in the media of the main arteries. The muscular arteries showed similar histological changes to those described in Case 4, but these were much less severe and less widespread.

DISCUSSION

Symptomatology. Symptoms that have been reported in patients with patent ductus arteriosus and severe pulmonary hypertension are breathlessness on exertion, frequent chest infections, hæmoptysis, substernal pain, and cyanosis, and those of the present series are similar. Breathlessness on exertion which occurred in all the previously reported cases (Johnson *et al*, 1950; Campbell and Hudson, 1951; Bothwell *et al*, 1952; Dammann and Sell, 1952; Cosh, 1953; Hultgren *et al.*, 1953; Smith, 1954), was a symptom of all patients in the present series. Dammann and Sell (1952), found that recurrent attacks of pneumonia were common in their patients and, although none of the present patients gave a history of pneumonia, seven of them suffered from recurrent attacks of

pulmonary infection and the other had chronic asthma. Two of our cases had hæmoptysis and this also occurred in patients reported by Campbell and Hudson (1951) and Johnson *et al.* (1950). Hultgren *et al.* (1953) noted attacks of substernal pain on exertion in three of their eight patients while Smith's (1954) patient complained of a tightness over the præcordium on exertion. None of the present patients had chest pain but the one with asthma had tightness in the chest. In four of the five adults in the present series and in the patient reported by Campbell and Hudson (1951), cyanosis was so marked as to be discernable by them. The symptoms described above occurred with such frequency in patients with this anomaly as to be considered characteristic of it, but they are not pathognomonic of it since similar symptoms are a feature of other congenital defects such as atrial septal defect, ventricular septal defect, anomalous pulmonary venous drainage or Eisenmenger's complex, and are probably due to pulmonary hypertension associated with these lesions.

Signs. The striking feature of this group of patients, on clinical examination, was pulmonary hypertension which was recognized in all cases by its classical signs. Although previous authors have noted the loud split second pulmonary sound (Campbell and Hudson, 1951; Cosh, 1953; Hultgren *et al.*, 1953; and Smith, 1954), and Bothwell *et al.* (1952) have described a "forceful epigastric pulsation," they have not mentioned other signs of pulmonary hypertension and it has not been emphasized that these signs are an essential feature of the present anomaly. In any patient with such clinical signs a diagnosis of patent ductus arteriosus and pulmonary hypertension should always be considered in the differential diagnosis.

Five of the eight patients in the present series had abnormally high pulse pressures. This was also a feature of some patients described by Dammann and Sell (1952) but they considered the pulse pressure of little diagnostic aid, since they also observed abnormally high pulse pressures in many of their patients with ventricular septal defects while a normal pulse pressure occurred in one of their patients with a patent ductus arteriosus.

The intensity and distribution of cyanosis with this congenital lesion depends upon the degree of reversal of the shunt. Generalized cyanosis occurs when there is a marked right-to-left shunt causing arterial blood oxygen unsaturation and subsequent polycythæmia. Such generalized cyanosis was present in the case of Campbell and Hudson (1951), in the first patient of Cosh (1953) and in Cases 2, 4, 5, and 8 in the present series, who were also polycythæmic. Case 4 was, in fact, admitted to hospital with a diagnosis of polycythæmia rubra vera. Cyanosis was restricted to the lower extremities in Cases 1 and 7 and was more obvious after exercise. Cosh (1953) reported this distribution of cyanosis in his second case. There was no cyanosis in Cases 3 and 6 of the present series, nor in Cosh's (1953) third case. Although cyanosis restricted to the lower extremities is usually regarded as a sign of coarctation of the aorta associated with patent ductus arteriosus, it is more correctly a sign of pulmonary hypertension associated with patent ductus arteriosus. This sign occurs in patients with the latter combination in the absence of coarctation of the aorta, while it does not occur in patients with coarctation of the aorta and patent ductus arteriosus unless there is also pulmonary hypertension sufficient to produce a flow of unsaturated blood from pulmonary artery to aorta. Although it is apparent that cyanosis may or may not be associated with the present anomaly it is of the greatest importance as a diagnostic sign when restricted to the lower extremities.

The murmurs noted at the base of the heart in the present group of patients are in accord with those reported by previous observers. Two of our patients had a basal systolic murmur, one a basal systolic murmur and a diastolic murmur, one a basal diastolic murmur only, one a Gibson murmur, and three had no murmurs. A Gibson murmur is an uncommon feature of patent ductus arteriosus when there is associated pulmonary hypertension and in the present series such a murmur was heard only in Case 1, who had also coarctation of the aorta. These unusual auscultatory findings are a manifestation of an abnormal blood flow through the patent ductus arteriosus. Only a basal systolic murmur was present in fifteen patients reported by Dammann and Sell (1952) and these observers suggested that this was due to the flow through the ductus occurring only in systole. Johnson *et al.* (1950) and Campbell and Hudson (1951) noted that the dominant basal murmur

was in diastole and these latter observers thought that it was probably the murmur of pulmonary incompetence. Since murmurs were absent in three of our patients where there was still evidence of blood flow through the patent ductus arteriosus, from cyanosis in the systemic circulation, it was thought that the large size of the patent ductus arteriosus accounted for the absence of murmurs. With the exception of a Gibson murmur, which is rare, basal murmurs are of little diagnostic importance in this anomaly since it may present only a systolic murmur, only a diastolic murmur, a systolic murmur and diastolic murmur, or, indeed, no murmurs. Four of our patients had mitral diastolic murmurs and Dammann and Sell (1952) noted this murmur in 10 of their 15 patients. Since one of our four patients with a mitral diastolic murmur had, at autopsy, organic mitral stenosis, it seems possible that such a mitral diastolic murmur may be a sign of associated mitral stenosis.

The electrocardiogram provides confirmatory evidence of right ventricular hypertrophy which is a diagnostic feature of the anomaly. All eight patients in the present series had striking evidence of right ventricular hypertrophy (Fig. 1 and 2) and this has been noted in most previously reported series.

On radiological examination, all the patients in the present series have shown evidence of cardiac enlargement, particularly of the right side, and increased prominence of the pulmonary artery and its main branches (Table II and Fig. 3 and 4). In six of the eight patients there was increased pulsation of the pulmonary arteries but in none did this amount to a hilar dance. These signs, which are in keeping with those described by the authors quoted previously, are characteristic of, but not diagnostic of, the present anomaly. Patients with the classical features of an atrial septal defect, ventricular septal defect, and mitral stenosis with severe pulmonary hypertension will probably not be confused with the anomaly under discussion on radiological examination, but in less characteristic cases with these lesions and in patients with Eisenmenger's complex, the radiological appearances may be identical with those found with a patent ductus arteriosus and pulmonary hypertension. Patients with an atrial septal defect usually have a more marked pulsation in the pulmonary arteries amounting to hilar dance and greater cardiac enlargement. A ventricular septal defect usually causes more marked left ventricular hypertrophy than has been observed in patients in this series. The degree of left atrial enlargement will usually allow patients with mitral stenosis and pulmonary hypertension to be differentiated from the present anomaly, but this is sometimes impossible since mitral stenosis may occur in association with patent ductus arteriosus and pulmonary hypertension. It also appears probable that many patients diagnosed on clinical and radiological examination as cases of idiopathic pulmonary hypertension are, in fact, examples of the present anomaly or of other congenital septal defects, complicated by pulmonary hypertension.

Angiocardiography will provide confirmatory evidence of a patent ductus arteriosus when the pulmonary blood pressures are sufficiently high to cause the blood to flow from the pulmonary artery to the aorta. Films taken two to three seconds after the injection show contrast medium passing from the right ventricle to the pulmonary arteries and thence into the descending aorta. In the present series, with the exception of Case 2, there was no difficulty in recognizing the source of the contrast medium in the descending aorta since there was no filling of the ascending portion (Fig. 5). In Case 2 there was early filling of the ascending aorta and this patient was considered to have an overriding aorta as well as a patent ductus arteriosus since such marked filling appeared incompatible with regurgitation of the dye into the ascending aorta (Fig. 6). Angiocardiography may be of value even in patients who are not cyanosed for, although the blood flow in such cases is not predominantly from pulmonary artery to aorta, there may be sufficient mixing of the blood for some of the dye to pass from the pulmonary arteries into the aorta as in Case 6.

Cardiac catheterization usually provides confirmatory evidence of a patent ductus arteriosus when associated with pulmonary hypertension. In all cases it demonstrates the pulmonary hypertension and in five of the six patients so investigated in this series the cardiac catheter passed through the ductus into the descending aorta. The ease with which the ductus was catheterized in this series and the frequency with which this has been reported in the series of Cosh (1953), Dammann and Sell (1952) and the case of Smith (1954) show this manœuvre to be a most valuable sign of the present anomaly. The ease of catheterization of the ductus is probably explained by its

large size and by a predominant blood flow from pulmonary artery to descending aorta. It is of interest to note that the only patient in the present series where the ductus was not catheterized was not cyanosed, and blood samples showed that the shunt was predominantly from aorta to pulmonary artery. It is obvious from the present series (Table I) and other reported cases that a patent ductus arteriosus with pulmonary hypertension may be associated with other anomalies, such as an overriding aorta, a ventricular septal defect, or mitral stenosis, which alone would be sufficient to produce pulmonary hypertension and intubation of the ductus may be the only proof of its existence. If the patent ductus arteriosus had not been catheterized, the diagnosis would have been one of ventricular septal defect alone in Case 3 and one of Eisenmenger's complex alone in Case 2. Examination of the oxygen saturation of blood samples helps in diagnosis. When the shunt is not completely reversed it is possible to recognize the patent ductus from the higher blood oxygen saturation in the pulmonary arteries than in the right ventricle, as in Case 6. When the shunt is reversed, arterial blood from the lower extremities is less saturated with oxygen than blood from the upper extremities but, although other authors have described this, it was not used as a diagnostic sign in any of our patients. When there are associated lesions such as an atrial or a ventricular septal defect they may be recognized from characteristic changes in the oxygen saturation of blood samples obtained at cardiac catheterization. When such anomalies occur it may be impossible to diagnose a patent ductus arteriosus from the blood samples. In Case 3, the blood oxygen saturations demonstrated a ventricular septal defect and a patent ductus arteriosus was only diagnosed because a catheter was passed through the ductus.

Discussion of Pathology

Certain pathological features appear to be characteristic of patent ductus arteriosus associated with pulmonary hypertension but since similar changes occur in other forms of congenital heart disease with a high pulmonary artery blood pressure such as Eisenmenger's complex, they cannot be considered pathognomonic of the present anomaly. Such features as right ventricular hypertrophy, dilatation of the main pulmonary artery, and prominence of the intrapulmonary vessels in cut section of the lung, which were present in both our autopsied cases and have been reported by Dammann and Sell (1952), and Hultgren *et al.* (1953), appear to be intimately related to pulmonary hypertension.

There was a large patent ductus arteriosus in both our cases examined at necropsy and this appears to be characteristic of a ductus associated with pulmonary hypertension since it has been noted previously by Johnson *et al.* (1950) and Dammann and Sell (1952). In Case 4 in our series there was widespread atheroma in the aorta and throughout the pulmonary arterial tree and in the ductus itself, while in Case 5, there was only an isolated plaque in the ductus. The marked difference in distribution of atheroma, observed in our two patients, is compatible with previous reports. Johnson *et al.* (1950) found it to be widespread throughou. the pulmonary arterial tree, tending to occur especially at certain sites as " impingement plaques," while Dammann and Sell (1952) found that atheroma may be absent.

Johnson *et al.* (1950) described medial changes in the pulmonary vessels as well as atheroma and stated that in these vessels there was " athero-sclerosis with large numbers of cholesterol-laden macrophages in the intima " and " fraying out and rupture of the elastic tissue of the media at focal points along the wall with aneurysm-like bulging of the intima at such points." In Case 5 of the present series, the walls of the pulmonary artery and aorta were involved by medio-necrosis, although not by atheroma (Fig. 13).

Old pulmonary arterial thrombosis which occurred in the left pulmonary artery and its branches in Case 4 is a complication that has been noted previously by Hultgren *et al.* (1953) and Smith (1954). This complication has not been a feature of all patients examined at autopsy since it was not present in Case 5 of this series and was not mentioned by Johnson *et al.* (1950) and Dammann and Sell (1952). Hultgren *et al.* (1953), in their description, stated that there were recent thrombi

showing early organization and others that were old showing recanalization. Smith (1954) thought that it was difficult to explain the ætiology of embolism leading to thrombosis in the pulmonary arteries as he found no evidence of endocarditis, endarteritis, or polycythæmia to account for it. Our patient with this complication was extremely polycythæmic.

The histological appearances described above in Case 4 are similar to those reported by previous authors. Dammann and Sell (1952) described medial thickening and severe intimal proliferation. Cosh (1953) found an increase in the muscle and elastic tissue in the media with occasional small raised plaques of fibro-elastic tissue in the intima of the arteries and medial hypertrophy and thickening of the intima in the arterioles. Campbell and Hudson (1951) noted hypertrophy of the adventitia and media with thickening of the intima. Johnson *et al.* (1950) described intimal proliferation and medial hypertrophy. The causes of these histological changes have been discussed by Hultgren *et al.* (1953). These latter observers believe that the vascular narrowing was not a direct complication of the patent ductus arteriosus and not due to prolonged increase in the total pulmonary blood flow, since they failed to find pulmonary vascular sclerosis in uncomplicated cases of patent ductus arteriosus and noted that aged patients with patent ductus arteriosus were free from pulmonary arterial lesions. Although they noted that it was possible in animals to produce an acute arteritis and thrombosis by injection of various substances and to produce a high pulmonary artery blood pressure by this means, they do not believe that pulmonary hypertension in the present anomaly followed pulmonary embolism since there was no clinical history of such an event. They accept the theory of Edwards (1953) who believes that pulmonary hypertension is due to persistence of the fœtal state of the pulmonary vasculature so that the final histological appearances are those of infantile pulmonary vessels with superadded changes resulting from the pulmonary hypertension.

Differential Diagnosis

The differential diagnosis of the present anomaly is from other cyanotic and acyanotic conditions associated with pulmonary hypertension. A long history of recurrent pulmonary infection and signs of pulmonary hypertension and cyanosis may suggest a diagnosis of chronic pulmonary heart disease but, as pointed out by Platts and Whitaker (1954), the absence of carbon-dioxide retention will exclude this.

The degree of polycythæmia may be so extreme as to mimic polycythæmia rubra vera but this can usually be excluded by the normal hæmatological findings in other than the red cell series and by complete cardiological examination.

The frequency of a mitral diastolic murmur with this anomaly causes it to be confused with mitral stenosis and pulmonary hypertension and it may be impossible to distinguish this without special investigation. The differentiation may only be made when an angiocardiogram shows simultaneous filling of the pulmonary arteries and descending aorta, when a catheter passes through a patent ductus, or when an increase in blood oxygen saturation is demonstrated in the pulmonary arteries.

Patients with classical signs of an atrial septal defect can be differentiated from those with the present anomaly by the small pulse volume, a more marked cardiac enlargement, and marked pulsation in the pulmonary arteries amounting to a hilar dance. Others with less typical clinical and radiological signs may only be recognized by demonstrating a left-to-right shunt in the atria in acyanotic patients or by passing a catheter through the atrial septal defect. Angiocardiographic examination will differentiate patients with atrial septal defect and reversal of flow by demonstrating early filling of the left atrium. A right bundle branch block pattern in the electrocardiogram will not differentiate the two conditions since this occurs with both.

Since the clinical, radiological, and electrocardiographic features of ventricular septal defect and Eisenmenger's complex may be indistinguishable from the present anomaly, these lesions are difficult to differentiate from it. An increase in blood oxygen saturation in the right ventricle

does not always indicate a ventricular septal defect since it may be the result of pulmonary incompetence associated with patent ductus arteriosus and pulmonary hypertension. However, as it is usually easy to pass a catheter through a patent ductus arteriosus when there is associated pulmonary hypertension, failure to carry out this manœuvre, where there is increased blood oxygen saturation in the right ventricle, suggests that the patient has a ventricular septal defect and not a patent ductus arteriosus with severe pulmonary hypertension. The problem of differentiating the present anomaly from a ventricular septal defect with pulmonary hypertension and from Eisenmenger's complex is made even more difficult by the fact that these lesions may co-exist, as in Cases 2 and 3.

Eisenmenger's complex will be diagnosed in a patient with pulmonary hypertension when, on angiocardiographic examination, there is simultaneous and early filling of the ascending aorta and pulmonary artery from the right ventricle but, even when this occurs, cardiac catheterization may subsequently demonstrate a patent ductus arteriosus, as in Case 2 in the present series. In such a patient, the possibility that the ascending aorta is filled by regurgitation of blood entering the aorta by a patent ductus arteriosus cannot be completely dismissed but such an explanation seems unlikely when there is a large amount of contrast medium in the ascending aorta (Fig. 6).

As many of the patients with the present anomaly present only symptoms and signs of pulmonary hypertension it seems probable that many so-called cases of idiopathic pulmonary hypertension are, in fact, examples of the present congenital lesion. During the time that we have seen these eight patients, we have seen no case of idiopathic pulmonary hypertension and this diagnosis is one which should only be made when autopsy proof is available.

Patients with Fallot's tetralogy with loud and even palpable sounds in the pulmonary area may be considered on clinical examination to have cyanotic congenital heart disease and pulmonary hypertension and, possibly, patent ductus arteriosus and pulmonary hypertension. Such patients are, however, easily differentiated by measurement of pulmonary artery blood pressures.

Treatment

There is not yet sufficient evidence available to allow dogmatic statements to be made about the place of surgical treatment in cases of patent ductus arteriosus complicated by pulmonary hypertension. Dammann and Sell (1952) feel that the presence of pulmonary hypertension is an added indication for surgical treatment of the patent ductus arteriosus and point out that such treatment may be life saving. Hultgren *et al.* (1953) consider that surgery is indicated when the shunt is dominantly left to right but feel that when reversal of the flow has occurred, ligation of the patent ductus arteriosus may be dangerous. In Cases 4 and 5 in the present series gross structural changes had occurred in the pulmonary arteries, suggesting that the pulmonary hypertension was irreversible and that surgery was contra-indicated. It seems probable that patients with generalized cyanosis, where the shunt is dominantly from the pulmonary artery to the aorta, will be unsuitable for any surgical treatment. It is important in other patients to assess the individual at the time of operation from recording the pulmonary arterial blood pressure. This also seems to be Brock's view, since Braun *et al.* (1954) reporting a patient treated surgically by him, state that he believes that, if after digital compression of the patent ductus arteriosus the pulmonary artery pressure drops, the ductus can be ligated with safety, but, if the pressure rises, closure of the abnormal communication may be dangerous.

Summary

Eight patients with patent ductus arteriosus and severe pulmonary hypertension are described and an account of the autopsy findings in two of these is given.

The features of this anomaly are sufficiently clearly defined for it to be regarded as a specific entity. Breathlessness on exertion, hæmoptysis, cyanosis, and recurrent chest infections were the common symptoms.

On physical examination, the most characteristic signs were those of pulmonary hypertension which was the only clinical diagnosis that could be made consistently in the present series.

Six of the eight patients were cyanosed and in two of these this was more marked in the lower extremities. Although cyanosis may or may not occur, it is of great diagnostic importance when confined to the lower extremities, since this sign is specifically one of patent ductus arteriosus with pulmonary hypertension, but may be exaggerated if there is associated coarctation of the aorta.

With the exception of a Gibson murmur, which is rare, basal murmurs are of little diagnostic importance in this anomaly since it may present with only a systolic murmur or only a diastolic murmur, a systolic murmur and diastolic murmur, or no murmurs.

All eight patients had electrocardiographic evidence of right ventricular preponderance and two had, in addition, a right bundle branch block pattern.

Radiologically, all the patients had cardiac enlargement, mainly due to right ventricular hypertrophy, and increased prominence of the pulmonary artery and its branches, with abnormal pulsation not amounting to hilar dance.

Angiocardiography showed early filling of the descending aorta from the pulmonary artery in five cases.

In five of the six patients investigated by cardiac catheterization the catheter passed through the patent ductus arteriosus into the descending aorta indicating that this manœuvre is of the greatest importance in diagnosis. Eisenmenger's complex, atrial or ventricular defects with pulmonary hypertension, and mitral stenosis with pulmonary hypertension may all appear indistinguishable from the present anomaly on clinical, cardiographic, and radiological examination and may be differentiated only by angiocardiography and cardiac catheterization.

At autopsy the patent ductus was abnormally large in both cases. On histological examination the pulmonary arteries showed changes typical of those found in patients with congenital heart disease and pulmonary hypertension. One case had medio-necrosis of the main pulmonary artery and aorta.

Surgical treatment is contra-indicated in patients with generalized cyanosis. In other cases treatment will depend on the assessment of the patient at the time of operation.

We are grateful to Dr. C. E. Davies and Professor C. H. Stuart-Harris for allowing us to report Cases 4 and 5 who were seen in the wards of the Professorial Unit of the Royal Hospital, Sheffield, and to Dr. J. L. Edwards for allowing us access to the pathological material in these cases. We would like to thank Miss E. K. Abbott, Consultant Radiologist, for facilities in the Radiological Department, City General Hospital, Sheffield, and Mr. Nichols and Miss N. Hardy for technical assistance. We also wish to thank Mr. A. S. Foster, Artist to the United Sheffield Hospitals, and Mrs. Rose of the Photographic Department of the Royal Hospital, Sheffield.

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CALIBRATION OF AN ELECTRONIC PHONOCARDIOGRAPH

BY

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Calibration of a phonocardiograph is more difficult than calibration of an electrocardiograph and the clinical value of the procedure is less obvious. The loudness of the heart sounds and murmurs at the front of the chest does not depend exclusively on cardiac activity but is influenced also by the position of the heart in the chest, by the nature and thickness of the chest wall, and by extraneous factors related to disease of the lungs, pleura, or pericardium. For a valid comparison of phonocardiographic with auscultatory findings it is, however, essential to have some indication on the phonocardiogram of the absolute loudness of heart sounds and murmurs at the chest wall.

In logarithmic phonocardiography (Rappaport and Sprague, 1942) the low-frequency vibrations are selectively attenuated as they are in auscultation by the human auditory mechanism: the amplitude of the deflections on a logarithmic phonocardiogram are therefore directly related to the loudness of the audible sounds. In linear phonocardiography, without this low-frequency attenuation, the audio-frequency heart sound vibrations are masked on the record by lower-frequency vibrations of much greater amplitude: the deflections on a linear phonocardiogram thus correspond to palpable pulsation or thrills rather than to auditory phenomena. In stethoscopic phonocardiography an attempt is made to include the distortion of sound normally introduced by a stethoscope, without the distortion due in auscultation to the human ear. Because the stethoscopic phonocardiogram is an arbitrary recording, not corresponding to any sensory phenomenon, we do not favour it.

Methods

The earliest effective attempt at calibrated phonocardiography was that of Mannheimer (1940, 1941), who recorded sound phenomena in six frequency ranges. Mannheimer calibrated his own microphone, using the piston-phone technique described by Olson and Massa (1934).

For the study of basal diastolic murmurs, Wells *et al.* (1949) recorded at the end of each phonocardiogram a signal corresponding to a standard sound at 500 cycles per second and 80 decibels above an arbitrary threshold of audibility. Counihan *et al.* (1951), for the investigation of low-frequency præcordial vibrations, increased the standard signal to 90 decibels above this threshold. Dunn and Rahm (1952) calibrated their microphones with a piston-phone. Besterman and Harrison (1953) recorded a 50-cycle signal.

We have designed a calibration device for use with an electronic phonocardiograph already described in this Journal (Campbell *et al.*, 1952). A similar device could be fitted to the input stage of any other electronic phonocardiograph.

Choice of Calibration Signal. A standard frequency of 50 cycles per second was chosen because our investigations have been of heart sounds rather than of murmurs; for the latter a higher frequency might be preferable but this would involve a much more complex calibration device. We believe that described here to be suitable for general purpose phonocardiography.

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According to Fletcher (1948) the auditory threshold at 50 cycles per second is 0·35 dynes per sq. cm.: according to Wood (1940) it is 0·30 dynes per sq. cm. Our arbitrary threshold (0·33 dynes per sq. cm.) approximates to the mean of these: our standard signal, 25 decibels above this threshold, represents a sound which would be clearly audible under normal clinical conditions.

Present Instrument. Our microphone has been calibrated by the National Physical Laboratory: from their calibration we know that our standard signal corresponds to an output of 2·4 mV from the particular crystal microphone used for this investigation. The validity of this calibration, of course, depends on constant sensitivity of the microphone. Dunn and Rahm (1953*a*, *b*) found that the sensitivity of a piezo-electric crystal microphone remains very constant for at least two years.

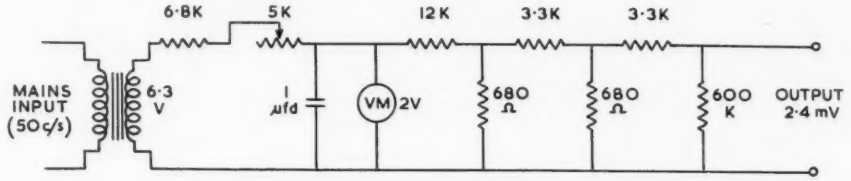

FIG. 1.—Circuit of calibrator unit. Resistor values in Ω (ohms) and K (10^3 ohms). V, volts; mV, millivolts; VM, voltmeter.

Fig. 1 shows the circuit of the device. The 50 cycles/sec. mains supply is stepped down by a filament transformer to approximately 6·3 V, and is then further reduced and set to exactly 2·0 V by a variable resistor and voltmeter, both mounted on the front panel. This allows compensation to be made for fluctuations in mains voltage. A capacitor is mounted across the voltmeter to form, with the voltage-dropping resistors, a simple resistance-capacitor filter, which eliminates high-frequency interference and discriminates against harmonic distortion in the incoming wave-form. With a linear amplifier this distortion would not be significant but, when logarithmic filters are inserted, the harmonic content of the lower frequencies is greatly emphasized; this excessive distortion would affect the apparent size of the calibration envelope.

A three-stage 600 Ω ladder network of high-stability resistors reduces the 2·0 V input to an injection level of 2·4 mV. Under test an input increased to 20·0 V gave an output of 24·0 mV, which was large enough for accurate measurement on an oscilloscope.

RESULTS

Fig. 2 shows logarithmic and linear phonocardiograms from a normal subject. For the logarithmic records the gain is high but the standard signal, being of low frequency, is attenuated by the filters in the preamplifier. For linear phonocardiography the gain is much reduced and the filters are out of circuit; at 50 cycles per second these effects tend to cancel out, so the standard signal is of the same order of amplitude on both logarithmic and linear records.

Fig. 3, from a patient with patent ductus arteriosus, shows how the calibrated record gives an indication of the loudness of the sounds and murmurs. The logarithmic phonocardiogram from the mitral area shows a systolic murmur of low amplitude, although the calibration signal is quite large, showing high gain on the instrument. At the pulmonary area the murmur is of greater amplitude in spite of a lower gain setting, shown by the small calibration signal.

Fig. 4 is a logarithmic phonocardiogram from a patient with mitral stenosis: this was recorded at low gain because of the loud heart sounds and an audible mid and late diastolic murmur fails to appear on the record. Fig. 5 is from a patient with advanced pulmonary emphysema: by reference to the standard signal the sounds, recorded at high gain, are seen to be faint.

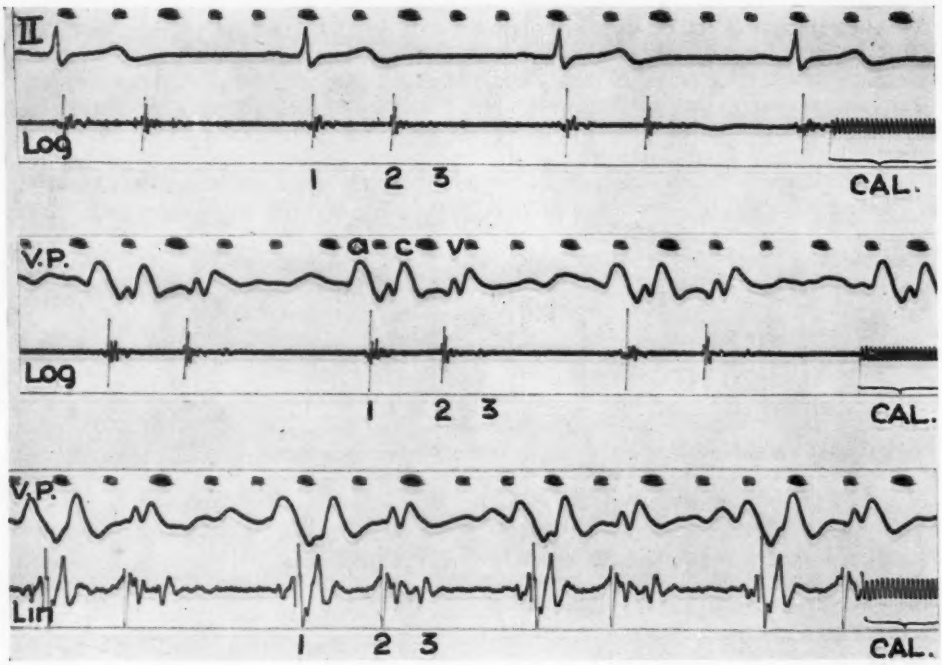

FIG. 2.—Calibrated phonocardiograms from the mitral area of a healthy subject. II, electrocardiogram (lead II); V.P., jugular venous pulse; a,c,v, waves of venous pulse; Log, logarithmic phonocardiogram; Lin, linear phonocardiogram; 1,2,3, heart sounds; CAL, calibration signal. In this and in subsequent records the calibration signal corresponds to a sound at 50 cycles per second exerting a pressure of 5·9 dynes per sq. cm. on the microphone; this is 25 decibels above the threshold of audibility. The time markings at the top of this and subsequent records are at 1/5 sec. intervals.

DISCUSSION

Clinically it is impracticable to run a phonocardiograph at constant gain, as is usual with an electrocardiograph. Since the amplitude of the loudest heart sounds is of the order of forty times that of the faintest ones that can be heard (Williams and Dodge, 1926) it is necessary to adjust the gain of the instrument to the loudness of the sounds in order to record the vibrations on a narrow strip of photographic material: this may bring up on the record a heart sound or murmur, which is inaudible, or may eliminate from the record an audible phenomenon. This discrepancy between auscultatory and phonocardiographic findings is inevitable with most phonocardiographs, but the situation is clarified if a standard signal is recorded after the phonocardiogram. The amplitude of the deflections of the standard signal depends on the existing gain and filter settings, and the absolute loudness of heart sounds and murmurs may be calculated by reference to an appropriate signal.

SUMMARY

A simple calibration device is described, which may be applied to the input stage of an electronic phonocardiograph. A standard signal, corresponding to a pure tone at 50 c/s and 25 decibels

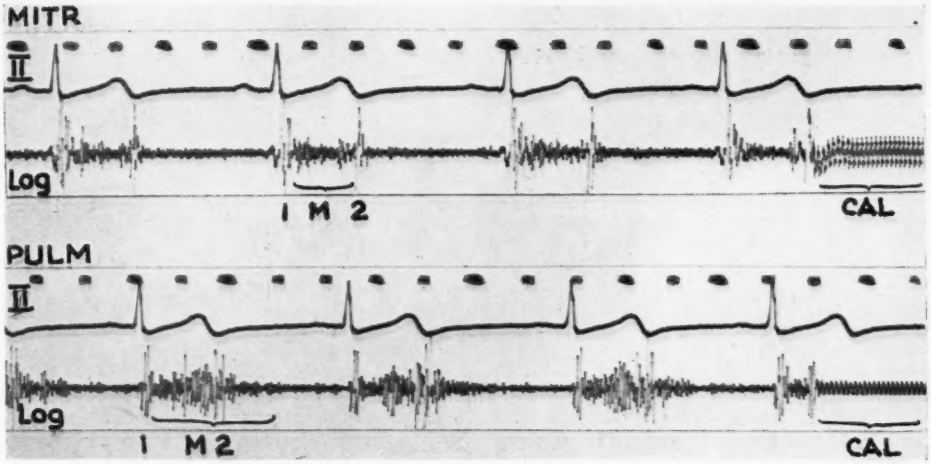

FIG. 3.—Calibrated phonocardiograms from a patient with patent ductus arteriosus. MITR, record from mitral area; PULM, record from pulmonary area; M, murmur. At the mitral area, in spite of high gain on the phonocardiograph, the murmur is not of great amplitude; at the pulmonary area the murmur is of much greater amplitude in spite of reduced gain on the instrument, shown by the small calibration signal.

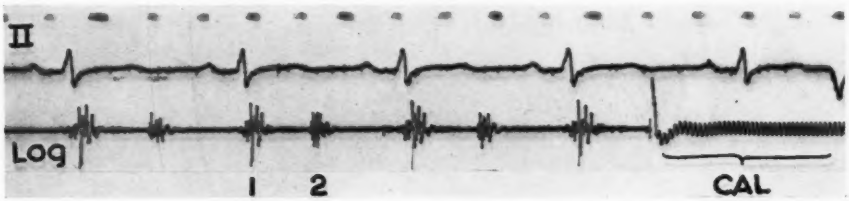

FIG. 4.—Calibrated phonocardiogram from the mitral area of a patient with mitral stenosis. By comparison with the small signal the sounds are seen to be loud; at this low gain a diastolic murmur, which was clearly audible, is not visible on the record. With the gain necessary to show the murmur the deflections corresponding to the heart sounds would be too large for their whole amplitude to be recorded.

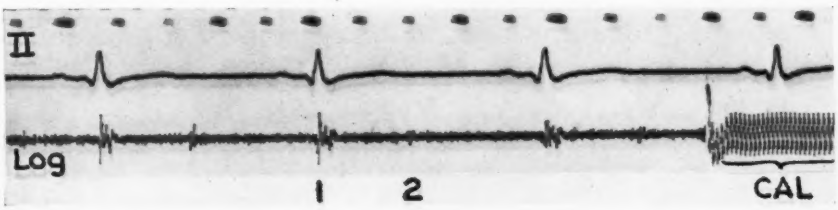

FIG. 5.—Calibrated phonocardiogram from the mitral area of a patient with pulmonary emphysema. The heart sounds are faint by contrast with the signal.

above the threshold of audibility at this frequency, is recorded at the end of each phonocardiogram. The amplitude of this signal is an indication of the absolute loudness of the sounds at the point of application of the microphone to the chest wall.

We acknowledge our indebtedness to the Rankin Medical Research Fund of the University of Glasgow for defraying expenses and to Mr. J. Brown for technical assistance.

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THE EARLY DIASTOLIC SOUND OF CONSTRICTIVE PERICARDITIS

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Evans and Jackson (1952), in 27 out of 30 cases of constrictive pericarditis, found an adventitious sound in early diastole which they ascribed in some to splitting of the second sound and in others to a third heart sound. Further research, however, has suggested that this added sound is probably a sound peculiar to constrictive pericarditis (Evans, 1954).

Potain (1856) described an added sound in early diastole in constrictive pericarditis in these words:

"The second sound was reduplicated or rather composed of two sounds, following one another in quick succession; one, clear, dry, ringing, with the usual characteristics of a valvular snap and of more or less unchanging intensity; the other coming immediately afterwards, less well defined, less resonant, coinciding exactly with the impulse felt in the præcordial region, like the impulse increasing during inspiration, and taking on at that point a rather metallic tone."

Lian *et al.* (1933) named the sound the pericardial protodiastolic vibration. Eliasch *et al.* (1950) showed that the sound coincided with the nadir of the early diastolic dip, recorded in right heart pressure records in constrictive pericarditis. More recently McKusick (1952), with simultaneous records of heart sound and ventricular border electrokymograms demonstrated that the sound coincided with an abrupt halt in rapid ventricular filling in early diastole. The purpose of the present study was to investigate further the clinical significance and pathogenesis of this sound.

METHOD

In 22 patients with constrictive pericarditis the heart sounds were examined clinically and in the phonocardiogram, and all patients were subsequently treated by operation. There were 19 men and 3 women in the series, with an average age of 36 years. Auricular fibrillation was present in eight cases. Phonocardiograms were recorded on a four-channel phonocardiograph using crystal microphones, as described by Leatham (1949). In 15 patients pre- and post-operative phonocardiograms were obtained. Right heart catheterization was performed before operation in six patients, using a capacitance electromanometer, critically damped, and a two-channel direct recorder. Simultaneous phonocardiograms and pressure records were obtained in five patients, the two records being made on separate instruments and synchronized by an electrocardiogram, which was used as a common reference tracing. Control experiments showed that no significant error in timing was introduced by the synchronous use of these two separate instruments.

RESULTS

An early diastolic sound was present before operation in 18 out of the 22 patients (Fig. 1). It was best heard over the centre of the præcordium and varied considerably in intensity. When loud it often had a snapping quality; it might be louder even than the first and second heart sounds. It

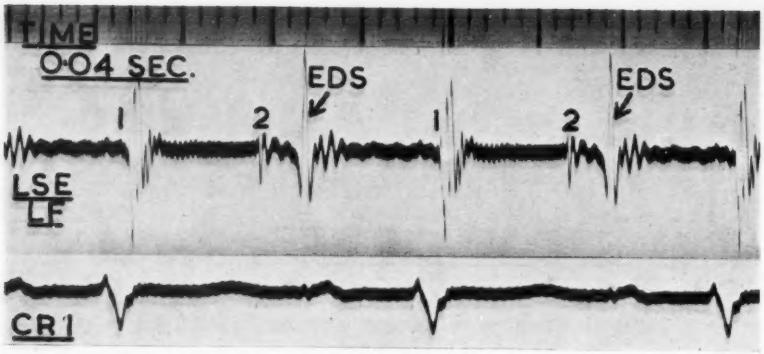

FIG. 1.—Phonocardiogram of the early diastolic sound, before operation. The early diastolic sound (EDS) is of comparable intensity to the first heart sound (1) and of greater intensity than the second sound (2) The interval between the beginning of the second sound and the peak of the deflection of greatest amplitude in the early diastolic sound is 0·1 sec. LSE = Left sternal edge. LF = low frequency. CR_1 = Electrocardiographic lead CR_1.

was often accompanied by a palpable diastolic thrust, as described by Potain (1856) and Wood (1950), and on a simultaneous phonocardiogram and apex cardiogram the sound was seen to coincide with this thrust. On inspiration the sound usually increased in intensity. In measuring the place of the sound in the cardiac cycle, the peak or nadir of the single vibration of greatest amplitude and/or highest frequency in the early diastolic sound was used, as a convenient point to measure. The place of the sound appeared to be the same as that of the opening snap of mitral stenosis, but the phonocardiogram in 15 patients before operation showed that the interval between it and the beginning of the second sound lay between 0·09 and 0·13 sec., the average being 0·1 sec., whereas the range for the opening snap was between 0·03 and 0·12 sec., with an average of 0·07 sec. (Mounsey, 1953).

After a successful operation, the sound became softer and was delayed so that it resembled the third heart sound both in its character and its place in the cardiac cycle (Fig. 2). The lessened intensity of the early diastolic sound after operation appeared to be related to the fall in jugular venous pressure. In the four patients in whom the sound remained loud, the pressure remained

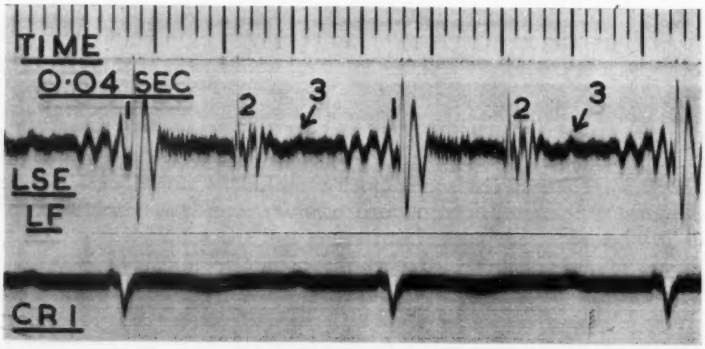

FIG. 2.—Phonocardiogram in the same patient as in Fig 1, after successful operation. The early diastolic sound has been replaced by a small third heart sound (3). The interval between the beginning of the second sound (2) and the peak of the third heart sound is 0·18 sec.

markedly raised, whereas in the two patients in whom the pressure fell to a normal level after operation, the sound was very soft. The interval between the beginning of the second sound and the early diastolic sound increased in every patient after operation and lay between 0·14 and 0·2 sec., with an average of 0·17 sec. It is unlikely that this marked change could be accounted for by the slightly reduced heart rate in six of the patients at the time of the postoperative phonocardiogram, since variations in rate appeared to have little effect on the timing of the sound in repeated phonocardiograms on the same patients. No direct correlation was noted between the amount of delay of the early diastolic sound postoperatively and the degree of fall of jugular venous pressure.

No clear early diastolic sound was heard before operation in four patients. They appeared comparable with the remaining 18 patients in regard to the height of the jugular venous pressure and the degree of liver enlargement. It was noted, however, in three of these four that the movement of the heart at operation differed from that seen in patients in whom an early diastolic sound was present. In patients having the sound, abrupt halting of ventricular expansion was seen in early diastole, while in the three patients without an added sound, ventricular dilatation in early diastole appeared less sudden and no abrupt halting was seen.

No direct correlation was noted between the presence of calcification of the pericardium and the early diastolic sound. Calcification was present in two of the four cases not having the sound and was very extensive in one, and absent in the other two. It was present in 11 of the 18 cases having the sound and absent or slight in the remaining seven.

The early diastolic sound is a useful clinical sign of constrictive pericarditis. It can be differentiated from a split second sound by its character, being less well defined and ringing, by its wide area of propagation, being usually widely heard over the whole præcordium, and by its timing, the interval between it and the beginning of the second sound being greater than that between the two components of a split second sound. A further point in recognition is that a split second sound is nearly always present in addition to the early diastolic sound, although admittedly often difficult to tell clinically. It differs from a third heart sound in that it is usually louder, more clear-cut, is heard over a wide area of the præcordium and is nearer in time to the beginning of the second heart sound than is the third sound. The increase on inspiration in intensity of the sound and in the coincidental diastolic thrust is a further guide to the recognition of the early diastolic sound.

The early diastolic sound is particularly useful in cases where pericardial calcification is not seen on X-ray examination, since here its presence may help to decide between heart failure and constrictive pericarditis. Infrequently the sound is absent in constrictive pericarditis so that this should not exclude the diagnosis.

The definite relationship between the lessening of the intensity of the sound after operation and the degree of fall of jugular venous pressure explains why this change in the sound predicts a favourable postoperative progress, as noted by Evans and Jackson (1952). In some patients, however, in spite of clinical improvement after operation, the sound remained loud, but in these the venous pressure did not return to a normal level.

Pathogenesis of the Sound. It was considered that this added sound in constrictive pericarditis is caused by an abrupt halting of rapid ventricular filling by the rigid constricting pericardium. In order to test this theory, simultaneous phonocardiograms and right heart pressure measurements, and pressure differences between the right heart and peripheral veins were examined.

In pressure records from the right ventricle and the right atrium, the early diastolic dip characteristic of constrictive pericarditis (Bloomfield *et al.*, 1946; Hansen *et al.*, 1951; and McKusick, 1952), was seen in the six patients examined by cardiac catheterization. In four both the right atrium and the right ventricle were entered, while in two, records were only obtained from the right atrium. The nadir of the early diastolic dip was approximately 0·01 to 0·02 second later in the atrium than in the ventricle. The early diastolic sound coincided closely with the beginning of the steep upstroke of the early diastolic dip in all four patients having the sound and in whom simultaneous sound and pressure records were taken (Fig. 3).

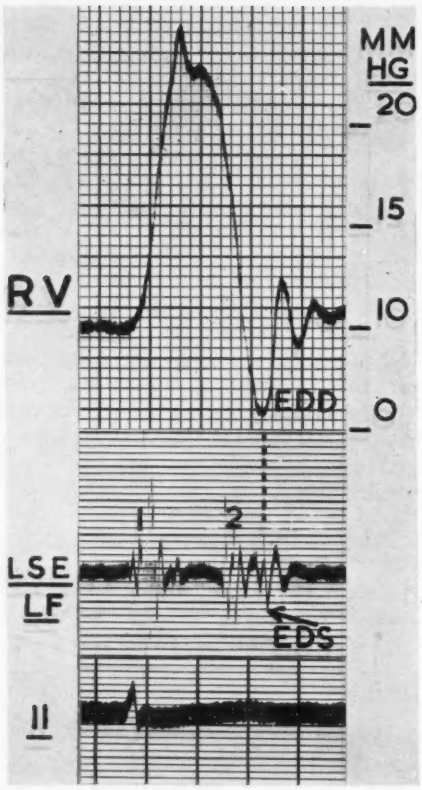

FIG. 3.—Simultaneous phonocardiogram and right ventricular pressure record. The early diastolic sound (EDS) coincides with the beginning of the steep upstroke of the early diastolic dip (EDD). RV=Right ventricular pressure. LSE LF=Phonocardiogram at left sternal edge with low frequency filter.

The pressure difference between the peripheral veins and right heart during the early diastolic dip was then examined in order to try and estimate variations in blood flow in early diastole. Pressure recordings from the superior vena cava, the left innominate vein, the subclavian vein, and the basilic vein were made in four patients, on withdrawal of the catheter from the right heart. Relative pressure during the cardiac cycle at this series of positions were reconstructed by the use of a synchronous electrocardiogram (Fig. 4). In this way it was shown that there existed during the first portion of the early diastolic dip, a rapidly increasing pressure difference, of graduated degree, at points between the basilic vein and the right ventricle. At the beginning of the steep upstroke of the early diastolic dip, when the sound occurred, this process was reversed and the pressure difference diminished rapidly. There was usually a small time lag of varying degree in the pressure dip in the distal veins compared with that in the right heart, as indicated by the slope of the dotted line in Fig. 4 and 5. A similar pressure difference was shown to exist between the inferior vena cava and the right atrium and ventricle, although in the case of the inferior vena cava there was an abrupt, as opposed to a gradual change, in the form of the wave on passing from the inferior vena cava to the right atrium.

These pressure differences between the right heart and the basilic vein suggest that, during the descending limb of the early diastolic dip, rapid ventricular filling is taking place, since the pressure difference is then increasing steeply, and that during the upstroke of the dip, filling rapidly decreases,

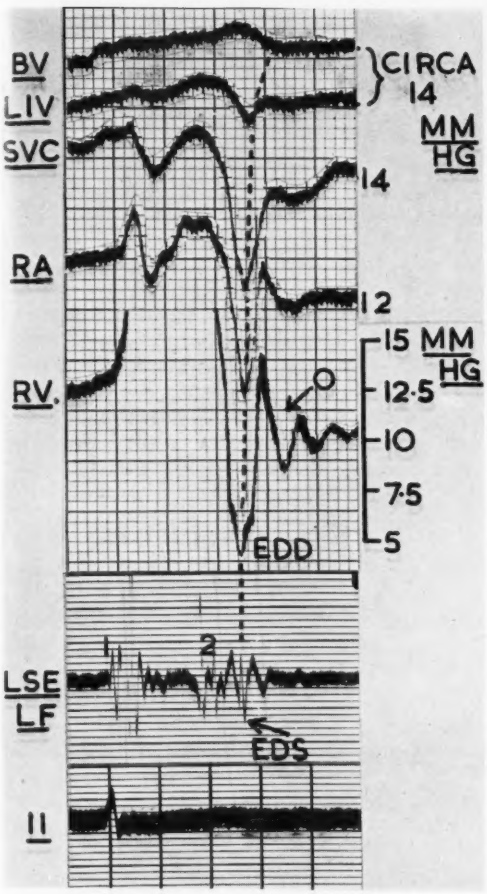

FIG. 4.—Synchronized pressure tracings from right ventricle (RV), right atrium (RA), superior vena cava (SVC), left innominate vein (LIV) and basilic vein (BV). The phonocardiogram (LSE.LF) was recorded simultaneously with the right ventricular pressure record and shows the position of the early diastolic sound (EDS).

The values for right ventricular pressures are shown on the right of the record. The scale for the other pressure tracings is the same, but, because of lack of space, only a single value is shown for each tracing at the point where it intersects the right-hand edge of the record.

The early diastolic dip (EDD) decreases in depth at greater distances from the heart until in the basilic vein no dip is recorded. Similarly the nadir of the early diastolic dip becomes slightly later in time, at greater distances from the heart, as indicated by the slope of the dotted line. Note the coarse oscillations (O) following the steep upstroke of the dip.

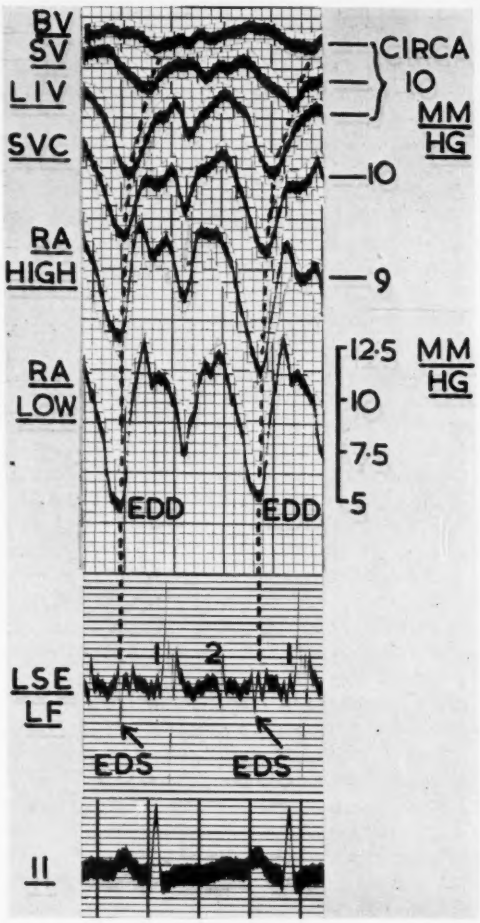

FIG. 5.—Synchronized pressure tracings from right atrium (RA) at points low and high within the atrium, superior vena cava (SVC), left innominate vein (LIV), subclavian vein (SV), and basilic vein (BV).

This graph was constructed in the same way as Fig. 4 and illustrates the same points, but with the difference that the delay in timing of the nadir of the early diastolic dip (EDD), at greater distances from the heart, is more marked in this patient than in the patient in Fig. 4. The delay is indicated by the slope of the dotted line.

since the pressure difference is falling abruptly. The abruptness of the halting of rapid filling is suggested by the very steep rise of pressure in the right ventricle and the coarse oscillations following it. The fact that the beginning of the rise in pressure in the right ventricle precedes that in the right atrium, superior vena cava, and innominate vein suggests that the sudden cessation in rapid filling originates in the ventricle.

These observations, therefore, indicate that the early diastolic sound is synchronous with the beginning of the steep upstroke of the early diastolic dip, and thus coincides with abrupt halting of rapid ventricular filling.

Collateral evidence that abrupt halting of rapid ventricular filling is the mechanism responsible for the early diastolic sound and the steep upstroke of the early diastolic dip was obtained from an experiment with a simple model, which is described in the appendix to this paper.

Absence of the Early Diastolic Sound. Absence of the sound in some patients was considered to be due to a slower ventricular filling and a less abrupt halting, an opinion supported by observations of the heart movements at thoracotomy. The difference noted in the form of the pressure records from the right heart in patients having the sound, as opposed to those without it, also supported this theory. In the four patients having the sound, the upstroke of the dip in right ventricular and atrial pressure curves was more abrupt and was followed in two of these by coarse oscillations. In the two patients not having the sound, on the other hand, the upstroke of the early diastolic dip was less abrupt and merged smoothly into a diastolic plateau, which was undisturbed by the coarse oscillations seen in the group of patients having the sound (Fig. 6).

Discussion

The evidence advanced in this study supports the concept of Hansen *et al.* (1951) and McKusick (1952) that the early diastolic sound in constrictive pericarditis is the result of abrupt halting of rapid ventricular filling by the rigid pericardium and is probably a waterhammer phenomenon. The exact mechanism of production of the sound, however, remains in doubt. Lian *et al.* (1933) suggested that the sound emanated from the vibrations of the calcified pericardium itself, when abruptly distended. Wood (1950) thought that it might be caused by the rapidly filling heart meeting the unyielding resistance of the pericardium which from a state of relaxation is thrown abruptly into tension. Eliasch *et al.* (1950) suggested that it resulted from turbulence in the right ventricle due to rapid filling.

Simultaneous phonocardiograms and right heart pressure records in this investigation have confirmed the finding of Eliasch *et al.* (1950), that the early diastolic sound coincided with the beginning of the steep upstroke of the early diastolic dip. In addition, however, pressure differences between the right heart, superior vena cava, left innominate vein, and basilic vein during the early diastolic dip have been measured in this study and these have added further evidence that the early diastolic sound coincides with abrupt halting of rapid right ventricular filling.

The early diastolic dip has been accepted as a real phenomenon in this investigation, although its nature and cause are still debatable. Wood *et al.* (1948) considered that it might be a distortion produced by their low frequency recording system. McKusick (1952) thought that the dip was probably a real phenomenon and that, while its pathogenesis was not fully understood, a ventricular sucking action, as a result of elastic recoil of the adherent pericardial casing, could not be excluded. Bloomfield *et al.* (1946) and Hansen *et al.* (1951), on the other hand, pointed out that the dip is also seen in cases of right heart failure due to any cause and in these cases ventricular suction as a result of pericardial recoil cannot be invoked to explain the dip.

It seemed to us that the problem was not so much why the dip occurred, since an abrupt fall of right ventricular pressure to near intrathoracic levels is likely to occur in early diastole, if ventricular relaxation is sufficiently rapid, but rather why the pressure in the more peripheral veins, such as the basilic vein, did not fall simultaneously. One factor that might explain this is the fact that the cross-sectional area of the total venous bed diminishes as blood flows centrally, from the peripheral vessels to the right heart (Green, 1943) and hence blood, entering the superior vena cava is in fact

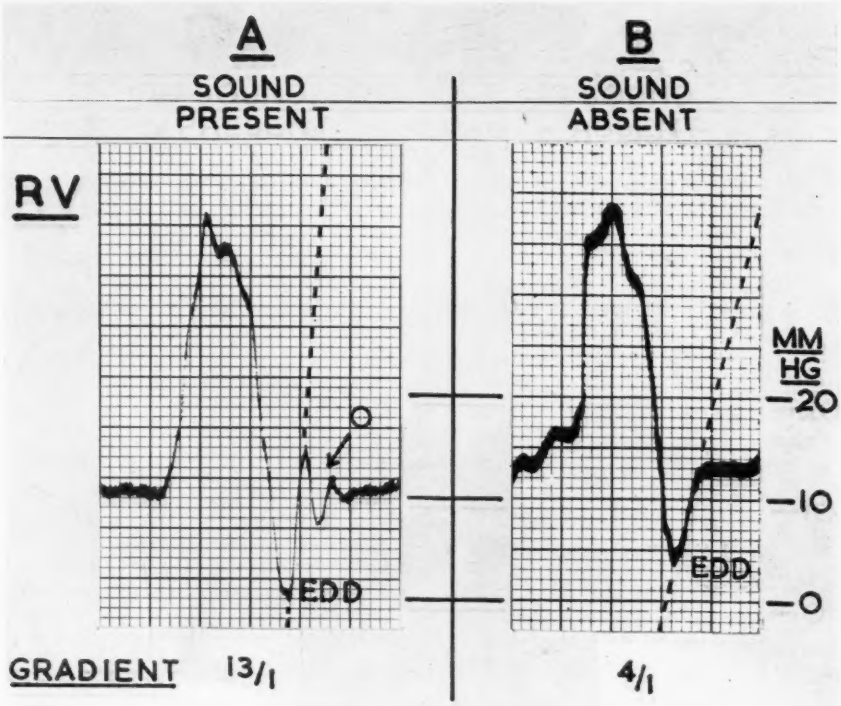

FIG. 6.—Comparison of the steepness of the upstroke of the early diastolic dip (EDD) in the right ventricle (RV), in patients with and without an early diastolic sound in constrictive pericarditis.
The dotted line indicates the gradient of the steepest part of the upstroke.
The steepness of the upstroke in patient A, having the sound (gradient 13/1), is contrasted with the gentler upstroke (gradient 4/1) in patient B, not having the sound. In addition coarse oscillations (o) followed the upstroke in patient A, having the sound, whereas these were absent in patient B, not having the sound.

entering a relative constriction. For this reason relatively large variations in pressure and flow in the venæ cavæ are accompanied by relatively small variations in the more peripheral venous bed.

The rise in pressure at the end of the early diastolic dip is almost certainly due to filling of the ventricle to near capacity, with the result that the pressure in the ventricle rises to the level of that in the peripheral veins. The finding that this rise of pressure was less abrupt and not followed by coarse oscillations, in those patients with constrictive pericarditis who did not have the sound, supports the idea that suddenness of halting of filling is necessary for the production of the sound. This would also explain why, in patients with right heart failure due to other causes, in spite of the presence of an early diastolic pressure dip, the loud early diastolic sound of constrictive pericarditis is not heard. In such patients halting of filling is less abrupt and is cushioned by the distensible myocardium, thus giving rise to a relatively soft third heart sound.

After successful operation, the main factors, causing a change in the intensity and timing of the early diastolic sound, were thought to be the removal of the rigid constricting pericardial casing, the consequent increase in diastolic heart volume and the decrease in venous filling pressure. Blood flows less rapidly into the ventricles in early diastole, because of the decreased venous pressure, and hence the sound produced by filling arrest tends to become softer and delayed. The increased

diastolic cardiac volume is a second factor that by prolonging ventricular filling tends to delay the sound. Lastly the partial removal of the rigid pericardial casing takes away to a large extent the mechanism responsible for sudden halting, which, as described above, is probably an essential factor in the production of the early diastolic sound. Thus, in cases where stripping has been extensive, the early diastolic sound, although it may have been prominent before operation, may become indistinguishable afterwards from a soft third heart sound.

It is possible and indeed probable that flow and pressure changes in the left heart also contribute to the genesis of the early diastolic sound. In this paper, however, in the absence of observations on the hæmodynamic events in the left atrium and ventricle, only the events in the right heart have been considered in relation to the genesis of the sound.

Summary and Conclusions

An added sound in early diastole was heard and recorded in the phonocardiogram in 18 out of 22 patients with constrictive pericarditis.

The early diastolic sound varied in intensity and character, but was often loud and snapping, and often accompanied by a palpable diastolic thrust. The average time interval between it and the beginning of the second sound was 0·1 sec.

After a successful operation of cardiac decompression, the sound always became softer and the average time interval between it and the second sound increased to 0·17 sec.

Simultaneous sound and pressure records from the right heart were obtained and the early diastolic sound was found to coincide with the beginning of the steep upstroke of the early diastolic pressure dip, characteristic of constrictive pericarditis. Pressure differences were measured between the right heart, the superior vena cava, and left innominate vein during the early diastolic dip. These observations indicated that the sound coincided with the abrupt halting of rapid right ventricular filling.

Evidence from right heart pressure records and from direct inspection of the heart at thoracotomy suggested that slower ventricular filling followed by less abrupt halting accounted for absence of the sound in some patients.

The early diastolic sound is a useful clinical sign and its presence supports the diagnosis of constrictive pericarditis. Its occasional absence, however, should not exclude the diagnosis.

An experiment described in an appendix supports the view that the early diastolic sound is due to abrupt halting of ventricular filling.

Appendix

An Experiment. The early diastolic sound, the early diastolic pressure dip and the pressure difference between the right heart and peripheral veins were imitated in a simple experimental model, in which abrupt halting of rapid ventricular filling was simulated (Fig. 7).

Water was led from a large reservoir, representing the total peripheral venous bed, through a pipe, representing the superior vena cava, into a collapsible but non-distensible rubber tube, representing the ventricle enclosed in a constricting pericardium. The pressure head in the reservoir was 30 mm. Hg and was constant throughout the experiment. The pipe was approximately 2 cm. in diameter and 30 cm. long. The capacity of the rubber tube, which could be closed at its distal end by a rubber membrane was 50 c.c. Pressure was measured in the rubber tube and reservoir by means of a cardiac catheter and simultaneous sound recordings were made with the microphone attached to the rubber membrane.

When no flow occurred in the system the pressure in the rubber tube was equal to that in the reservoir (Fig. 7A). When the rubber membrane was removed and steady flow occurred, the pressure in the tube approached atmospheric levels, while that in the reservoir remained unchanged (Fig. 7B). When a clamp was released from the end of the tube and the water accelerated from rest before reaching steady flow, a rapid fall in pressure in the tube took place, the pressure finally settling at the level previously recorded during steady flow (Fig. 7C).

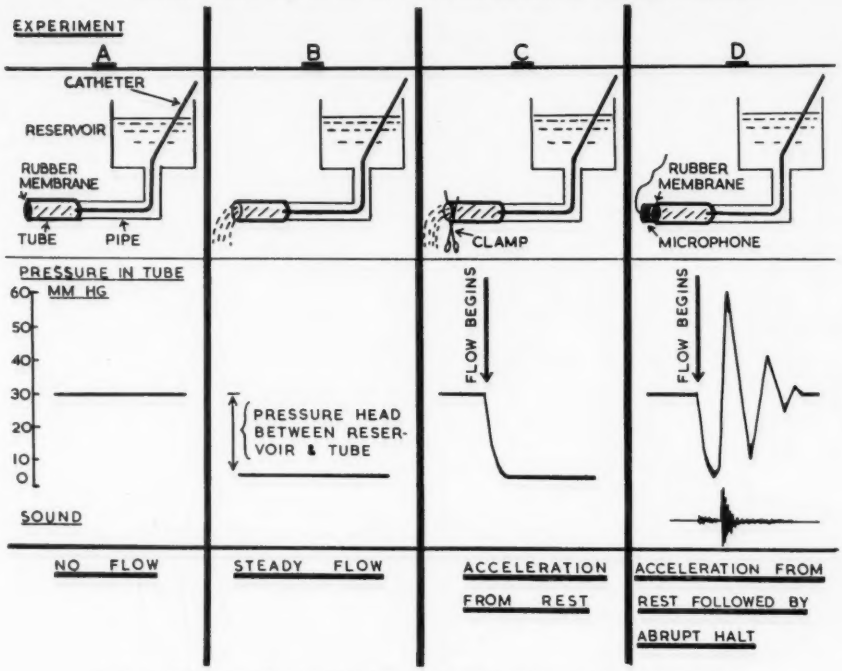

FIG. 7.—Diagram of an experiment. For explanation, see text of appendix.

In the final experiment (Fig. 7D), the end of the rubber tube was closed by the rubber membrane and the tube emptied by manual compression. The tube was then suddenly released and water flowed rapidly into it from the pipe, thus imitating ventricular filling in early diastole. Initially the same pressure changes were recorded in the tube, as when the water had accelerated from rest. Next when the closed tube had been entirely re-expanded by the water flowing into it from the pipe, there was an abrupt rise of pressure in the tube, followed by coarse oscillations, and a large sound was recorded at the beginning of this steep rise in pressure (Fig. 7D and 8). Finally, since flow had now ceased, the pressure in the tube returned to the level of pressure in the reservoir, which itself had remained unchanged throughout the experiment.

In this way, a pressure dip, followed by coarse oscillations was recorded, which was similar in broad essentials to the early diastolic dip and subsequent oscillations in the right ventricle in constrictive pericarditis. The sound produced in the experiment resembled the early diastolic sound in constrictive pericarditis in that both were coincident with the beginning of a steep rise in pressure terminating a pressure dip, which marked sudden arrest of rapid filling. In addition, the unchanged level of pressure in the reservoir which considerably exceeded the pressure in the tube during the pressure dip was comparable to the higher, relatively steady pressure in the basilic vein at the moment of the early diastolic dip in the right ventricle in constrictive pericarditis.

Conclusion. In a simple working model, in which water, under pressure, in a pipe fed from a reservoir, was allowed suddenly to flow into a small closed chamber, a sound, pressure variations and pressure differences between tube and reservoir were produced which resembled in broad essentials the early diastolic sound, the early diastolic pressure dip and the pressure difference between right heart and peripheral veins in constrictive pericarditis.

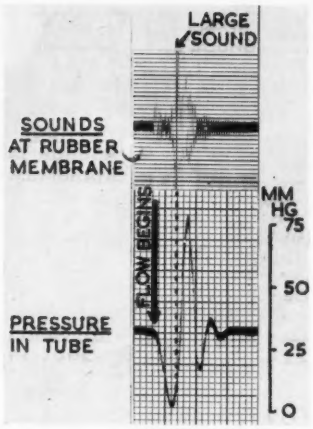

FIG. 8.—Simultaneous sound and pressure records obtained in Experiment D. The large sound is seen to coincide with the beginning of the steep rise in pressure.

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THE RESTING HYPERVENTILATION OF CONGENITAL HEART DISEASE*

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Existing knowledge of respiratory function in congenital heart disease is limited. Pioneer studies by Campbell *et al.* (1923) on four polycythæmic patients and one with pulmonary stenosis suggested an increase in resting ventilation, with compensatory decreases in the carbon dioxide fixing power of the blood. More recently, other workers (Bing *et al.*, 1948; Davison *et al.*, 1953; and Holling, 1952) have confirmed that there is a resting hyperpnœa in patients with a central venous-arterial shunt, but there have been no previous studies of respiration in other forms of congenital heart disease.

The present paper describes observations on the pattern of respiration in a number of forms of congenital heart disease, cyanotic and acyanotic. The pattern of external respiration has been examined, and an explanation of the observed hyperventilation has been sought in changes of carbon dioxide equilibria and of other variables affecting the respiratory system.

METHODS

Ventilatory Measurements. The resting ventilation rate, tidal volume, and respiratory minute volume have been obtained for a group of 91 patients by analysis of spirometer tracings. In a sub-group of 36 cases, the minute volume has also been determined by four Douglas bag readings. Generally there is a good correspondence between the two readings, although the spirometer tends to give a greater minute volume, since the patient is in this case breathing oxygen. Four resting alveolar samples were collected from each of the smaller group—two in the morning and two in the afternoon.

Cardiac Catheterization. The technique used in this hospital has been described previously (Holling and Zak, 1950). Arterial samples were collected anærobically in syringes lubricated with silicone fluid, and the *p*H measured at room temperature by means of a Stadie electrode system (Stadie *et al.*, 1930); values were corrected to body temperature by the method of Rosenthal (Rosenthal, 1948). The carbon dioxide content of each specimen was measured by the Van Slyke manometric apparatus. The serum carbon dioxide content and tension were estimated by means of nomograms (Van Slyke *et al.*, 1923 and 1928). For comparison with the alveolar gas samples, it was necessary to know also the composition of pulmonary venous blood, and in cases with a venous-arterial shunt the *p*H and carbon dioxide content found from the arterial specimen were corrected as follows.

Difference in *p*H arterial-pulmonary venous blood	$0.08f$ units
Difference in carbon dioxide content	$5.0f$ ml./100ml.

where f is the fraction of arterial blood derived from the right side of the heart.

* The work described in this paper has been submitted to the University of London in part fulfilment of the requirements of a Ph.D. degree in the Faculty of Science.

Subjects. Selection was governed simply by the degree of cooperation shown during the initial cardiac catheterization. To allow statistical treatment of the results, patients were divided into four groups.

(*a*) Central cyanotic, with venous-arterial shunt.
(*b*) Peripheral cyanotic, with reduced pulmonary flow.
(*c*) Acyanotic, with increased right ventricular pressure.
(*d*) Acyanotic, with increased pulmonary flow.

Pattern of External Respiration

Ventilatory Minute Volume. The resting minute volume seems increased in almost all cases of congenital heart disease, irrespective of whether the subject is cyanosed or not (Fig. 1). In assessing measurements of minute volume, it must be remembered that much depends on the success with which resting conditions are achieved. A usual figure for the young adult is about 4·0 litres/sq.m./min. (Baldwin *et al.*, 1948 and Matheson *et al.*, 1950), but it is easy to obtain higher values, and in a recent series of 27 cases the average value was 6·3 litres/sq.m./min. (Bucher, 1949). It was therefore decided to measure the minute volume in a group of nine normal subjects exposed to the same routine as the clinical material; the average value found was 4·2 litres/sq.m./min., which conforms closely with the lower standards.

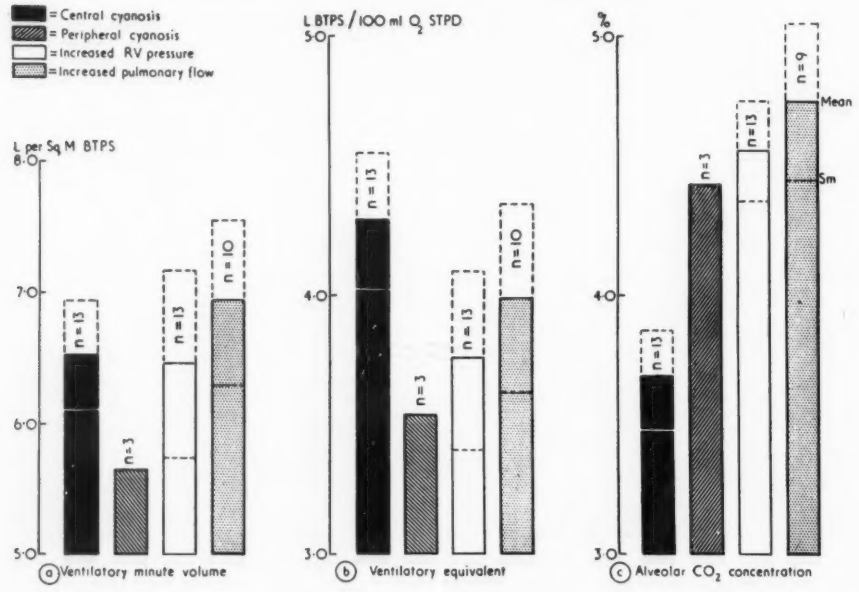

FIG. 1.—Minute volume, ventilatory equivalent, and alveolar carbon dioxide concentration in different types of congenital heart disease (39 cases). The mean and standard error are shown for each group.

Respiratory Rate and Tidal Volume. Having shown that the ventilatory minute volume is increased in the various forms of congenital heart disease, it is of some interest to consider the relative importance of changes in respiratory rate and tidal volume in the different conditions.

The rate varies considerably with age, and results have therefore been expressed as a ratio to the expected normal value, standards being based mainly on the work of Morse *et al.* (1949) who

studied a large group of adolescent boys. Three of the four groups of patients show a respiratory rate ratio that is within normal limits, but the group with an increased pulmonary flow shows a ratio of 1·23, the difference from normal subjects and other acyanotic patients (increased right ventricular pressure group) being statistically significant (Fig. 2).

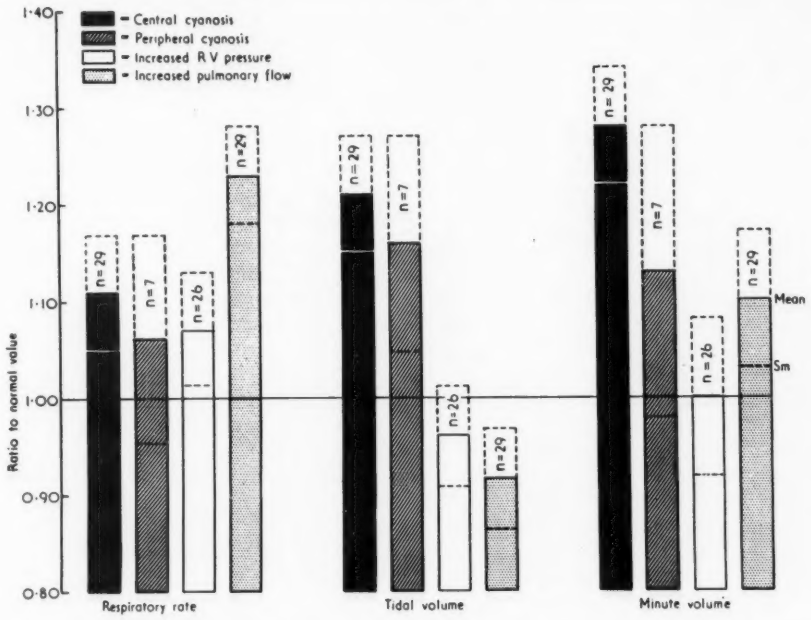

FIG. 2.—Pattern of respiration in congenital heart disease (91 cases). Respiratory rate, tidal volume, and minute volume expressed as ratio to normal values for subjects of same age and sex. The mean and standard error are shown for each group.

If tidal volume and total minute volume ratios are calculated in the same way, it can be seen that acyanotic patients with an increased right ventricular pressure show ratios that are close to unity. This is in keeping with the theoretical expectation that this group would correspond most closely with normal. Patients with an increased pulmonary flow show a smaller tidal volume, but there is still some hyperpnœa, as the shallow respiration is more than offset by a rapid respiratory rate. There is a striking difference between these two groups and the patients with cyanosis of either central or peripheral type, the cyanotic groups showing a considerable increase of tidal volume and total minute volume ratios.

Ventilatory Equivalent. Since the pattern of external respiration differs in the different classes of congenital heart disease, it is to be expected that there are corresponding differences in the efficiency of respiration in meeting the requirements of metabolism. The index taken for this purpose is the ventilatory equivalent.

The different classes of congenital heart disease show values ranging from 3·5 to 4·3 litres of ventilation BTPS per 100 ml. of oxygen STPD, and although the differences between the classes are not very large, it may be noted that higher values are observed in patients with increased pulmonary flow or central cyanosis. However, the main finding is that all classes show a greater ventilatory equivalent than the control value of 2·60 litres/100 ml. found in nine normal adults and

the previously reported standard of 2·78 litres/100 ml. (Matheson and Gray, 1950). It has been known for many years (Liljestrand, 1918) that at normal levels of ventilation a slow respiratory rate is the most efficient, and efficiency declines progressively as the respiratory rate is increased. It is therefore not surprising that there is a highly significant correlation (P=0·001) between respiratory rate and ventilatory equivalent in the congenital heart cases. Many patients have a greater respiratory rate than the normal adult, and this undoubtedly contributes to the increased ventilatory equivalent. In some the rate is high on account of adolescence, but in patients with an increased pulmonary flow the rate is still greater than normal even if allowance is made for age, and it would seem that other factors are helping to produce this less efficient pattern of respiration.

Changes in Carbon Dioxide Equilibria

Many of the cases of congenital disease show alterations of carbon dioxide equilibria. In some instances these are a secondary manifestation of the observed hyperpnœa, but in other cases they appear to be an important factor contributing to the increase of resting ventilation. Changes in the composition of alveolar gas and arterial blood are considered in turn.

Alveolar Carbon Dioxide Concentration. The congenital heart patients all show rather low alveolar carbon dioxide concentrations (Fig. 1), and several factors probably contribute to this. Many of the cases were children, and it is known (Haldane and Fitzgerald, 1905) that the alveolar carbon dioxide concentration is lower in childhood. In the present series, there was a fair correlation between age and alveolar carbon dioxide concentration (p=0·01). Voluntary hyperventilation immediately prior to collection of the samples was probably not of great importance, since there was no correlation between the alveolar carbon dioxide concentration and the level of resting ventilation. Samples may also have been delivered with varying efficiency, as the period of tuition was limited. However, most subjects show a satisfactory agreement between consecutive alveolar samples, and there is a good correspondence between the carbon dioxide concentration of alveolar gas and the carbon dioxide tension of pulmonary venous blood (Fig. 3). The average difference in carbon dioxide tension between the two phases is about 6 mm. Hg; 3 mm. of this gradient is related to systematic errors in the indirect method of measuring blood gas tension (Lambertsen *et al.*, 1953), and part at least of the remaining difference can be attributed to the use of inspiratory alveolar samples.

Taking into account these various factors, it would seem probable that in all forms of congenital heart disease except the central cyanotic group the alveolar carbon dioxide concentration is within normal limits. Even in the central cyanotic group, the shunting of carbon dioxide rich blood into the arterial system raises the arterial carbon dioxide tension to normal values, although the tension of pulmonary venous blood is below normal. Two factors tend to maintain the carbon dioxide tension in the face of a resting hyperventilation. These are an inefficient pattern of ventilation, particularly in patients with an increased pulmonary flow, and an inefficient pulmonary circulation in many of the cyanotic patients. However, it seems possible that there may also be changes in acid/base equilibria maintaining a normal arterial and an increased tissue tension of carbon dioxide in the face of increased ventilation, and these changes are considered below.

Acid/Base Equilibria of the Blood. The arterial pH in all forms of congenital heart disease is slightly to the acid side of normality (Fig. 5). This would suggest that changes in acid/base balance have more than compensated for the slight hyperventilation of rest, and it represents an adaptation of some physiological importance, for with exercise hyperventilation can exceed the normal level without producing an alkalosis.

The carbon dioxide content of arterial blood is reduced in all groups except those with an increased pulmonary flow. This is in keeping with the resting hyperventilation previously noted; the normal carbon dioxide content in patients with an increased pulmonary flow is probably related in part to the lesser degree of hyperventilation in the acyanotic cases, and in part to the inefficient pattern of ventilation in this particular group.

The arterial carbon dioxide tension does not differ greatly from normal in any of the congenital

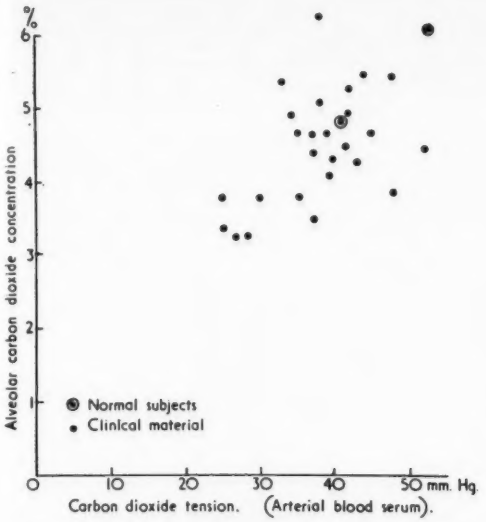

FIG. 3.—Relationship between alveolar carbon dioxide concentration and arterial carbon dioxide tension. Alveolar samples by Haldane method, arterial carbon dioxide tension by method of Rosenthal. There is a satisfactory correlation between the two measurements, slightly higher values being obtained by the Rosenthal method.

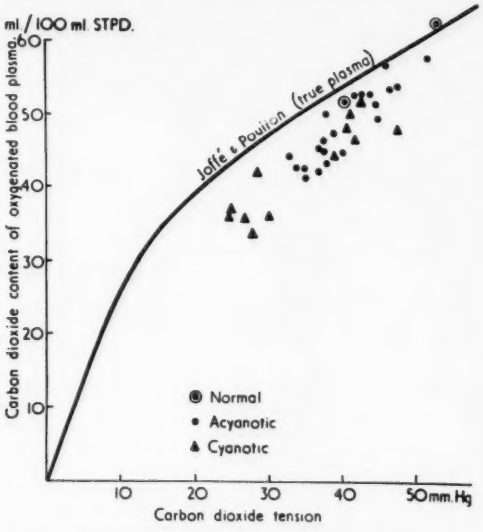

FIG. 4.—Carbon dioxide dissociation curve for arterial blood plasma. In patients with a venous-arterial shunt, the estimated pulmonary venous values have been substituted. The observed values are compared with a normal curve (Joffé).

heart patients, but within the acyanotic group there is a significant increase in tension with increased pulmonary flow, giving further evidence of inefficient ventilation in this group.

Carbon Dioxide Dissociation Curves. The clearest evidence of changes in acid/base balance can be found in a study of the carbon dioxide dissociation curves for arterial blood.

Values for two normal subjects and 33 cases of congenital heart disease are compared with a normal dissociation curve for oxygenated true plasma (Joffé and Poulton, 1920) in Fig. 4. It can be seen that while the normal subjects conform quite closely to this curve, the congenital heart patients deviate considerably, particularly in those cases where the arterial carbon dioxide tension is much reduced. The displacement of the carbon dioxide dissociation curve in a given subject shows some correlation with the level of hyperventilation in that subject (P=0·01–0·001), suggesting that the displacement does in fact represent an adjustment of acid/base balance that tends to compensate for the resting hyperventilation. It is interesting to note that for a comparable degree of hyperventilation, the displacement of the dissociation curve is greater in the cyanotic patients, suggesting that the degree of compensation is greater in these patients. The hæmoglobin levels were distributed fairly widely, extreme values being 8·8 and 18·7 g./100 ml., but within these limits there was no obvious relationship between displacement of the dissociation curve and the hæmoglobin level of the blood.

Importance of Changes in Carbon Dioxide Equilibria. It remains to be considered to what extent these changes in carbon dioxide equilibria are primary factors in maintaining a resting hyperventilation. In a number of conditions, there is clearly a tendency to tissue hypercapnia. A venous-arterial shunt may introduce carbon dioxide rich blood into the systemic circulation, there is the possibility of a sluggish systemic flow, although even in severe pulmonary stenosis this

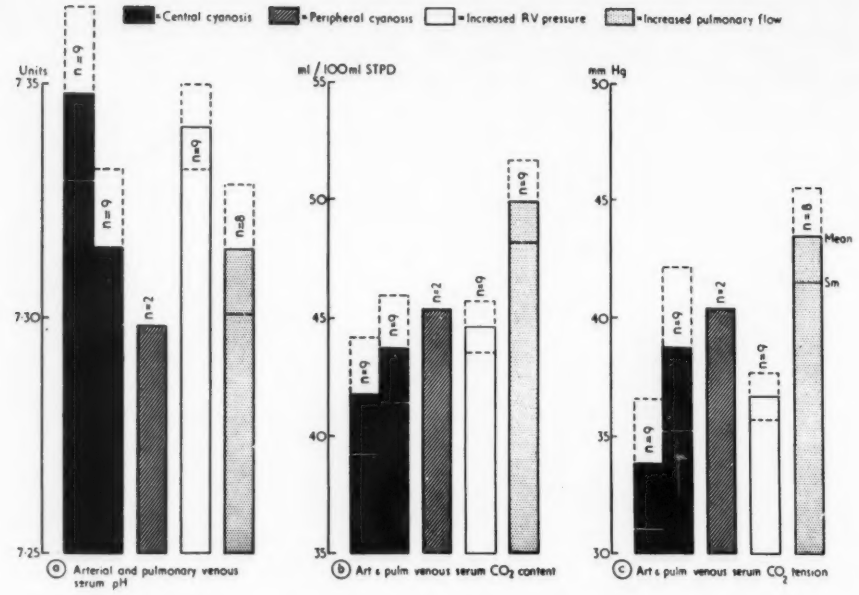

FIG. 5.—Chemical composition of arterial blood in congenital heart disease. In patients with a venous-arterial shunt (central cyanosis), the estimated composition of pulmonary venous blood is also shown. Mean and standard error indicated for each group.

is probably overcome to some extent by redistribution of the available cardiac output (Shephard, 1955), and there may be a tendency for carbon dioxide retention associated with an inefficient pattern of respiration. However, although the tissue carbon dioxide content may be normal or increased, the arterial carbon dioxide content is lowered, and an adjustment of acid/base balance is needed to keep the arterial carbon dioxide tension within normal limits. If tissue hypercapnia were the only factor maintaining the resting hyperventilation, an increased alkaline reserve might be expected, and the observed decrease suggests that other factors are of at least equal importance. A number of the other variables that may influence respiratory function are considered below.

OTHER VARIABLES AFFECTING RESPIRATORY FUNCTION

Oxygen Tension. The greater minute volume ratio observed in patients with central cyanosis (Fig. 2) suggests that oxygen lack is producing some stimulation of the respiratory system, probably through the activity of the chemo-receptors. However, in conformity with previous observations (Davison *et al.*, 1953), the correlation between arterial oxygen tension and minute volume ratio is very poor. It has been suggested recently (Bjurstedt, 1946, and Rahn and Otis, 1949) that the typical response to a maintained central hypoxia is a reduction in alkali reserve, and after 6–10 hours it is difficult to detect any increase of chemo-receptor discharge. However, even if there is a transfer of emphasis from hypoxia to a relative hypercapnia with maintained exposure of the respiratory system to low oxygen tensions, it remains convenient to consider the primary stimulus of oxygen lack as one feature that is contributing to the hyperventilation in patients with central cyanosis.

Medullary hypoxia does not seem of great importance in the resting state, although there is some evidence of medullary depression after exercise, such as the appearance of Mayer waves in the systemic blood pressure record (Shephard, 1954).

Pulmonary Blood Volume. The pulmonary blood volume has not been measured directly in the present series of patients, but an interesting correlation between tidal volume and pulmonary blood flow has been observed, and probably this can be interpreted as a respiratory response to a change in pulmonary blood volume. Previous workers (Rabinowitch, 1923, and Richards *et al.*, 1953) have described a decrease of vital capacity in conditions where pulmonary blood flow is increased, and in the present observations the tidal volume diminishes progressively as the pulmonary flow increases (Fig. 6).

The significance of this relationship has been tested in two ways. For the first test, observations have been divided into four arbitrary groups, according to the level of pulmonary flow, and the tidal volume has been compared in the four groups.

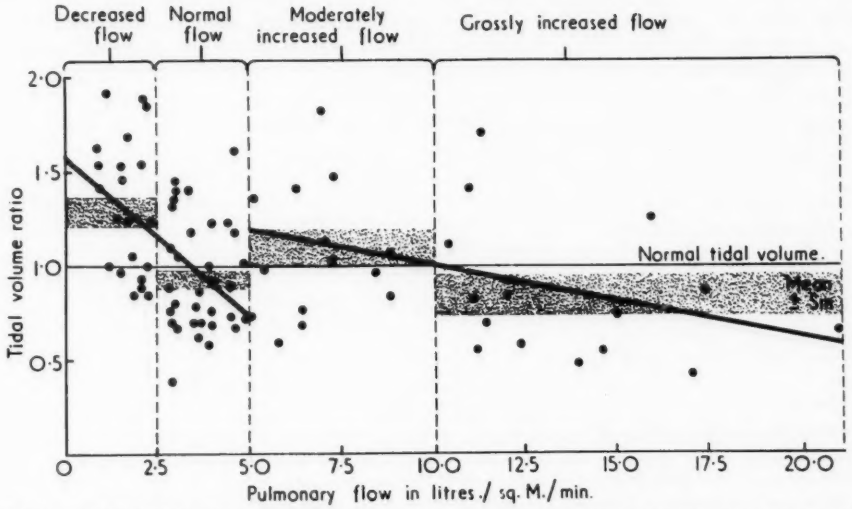

FIG. 6.—Relationship between tidal volume and level of pulmonary flow. According to the level of flow the 91 cases have been divided into four groups. The mean and standard error is shown for each group. Linear regressions fitted by method of least squares.

From this comparison, it is clear that the degree of correlation is very much greater in patients with a normal or decreased flow than in those with an increased flow. For the second test it was therefore decided to fit two linear regression lines, taking as an arbitrary dividing line a flow of 5 l./sq.m./min. The linear relationship is significant at both levels of flow ($P<0{\cdot}001$ and 0·05–0·02 respectively), and the difference between the two gradients is also highly significant.

It seems probable that the explanation of the principal relationship between tidal volume and pulmonary flow lies in associated changes of pulmonary blood volume. In the pulmonary circulation, increases of blood flow are typically associated with peripheral dilatation of small vessels rather than steeper pressure gradients between pulmonary artery and pulmonary vein (Ochsner, 1951), and a difference of blood volume may be expected in any condition where pulmonary flow is altered. It may be suggested that the increase of blood volume in turn alters the resistance of the lungs to expansion, causing the patient to adopt a rapid and shallow type of respiration. Similarly, if the pulmonary flow is less than normal the resistance of the lungs to expansion is decreased, and the tendency is to adopt the more economical pattern of slower and deeper respiration. However, other factors become involved in the correlation. In the central cyanotic group the magnitude of the right-to-left shunt is to some extent influenced by the level of pulmonary flow, and in the peripheral cyanotic group the degree of tissue hypoxia and associated hypercapnia is

largely dependent on the level of pulmonary flow. These additional factors are probably sufficient to explain the steeper gradient of the regression observed under the conditions of reduced flow.

Baro-receptor Discharge. The various forms of congenital heart disease show considerable differences of pressure relationships in the systemic and pulmonary circulations, and this could give rise to corresponding differences in the pattern of baro-receptor impulses reaching the respiratory centre. However, recent experimental work (Landgren, 1952, and Neil *et al.*, 1949) suggests that this factor is not of great importance. Observations on the carotid sinus have shown that the receptors discharge in response to a change of mean pressure, and if an increased pressure is maintained adaptation of the endings usually occurs. Other adaptive mechanisms, such as an alteration in the distensibility of the baro-sensitive area, or an alteration of sensitivity to these impulses in the medullary centres may also be brought into play, and it seems unlikely that the level of resting respiration is greatly influenced by these abnormal pressure relationships. Positive evidence to support this view is to be found in the pattern of respiration in patients with pulmonary stenosis. Here there is a gross increase of right ventricular pressure, and yet the pattern of respiration seems very normal (Fig. 2).

Circulation Time. The respiratory importance of the circulation time is that it gives a useful index of the degree of coordination between tissue requirements and the level of ventilation; if the transport of chemical stimuli to the respiratory centre is delayed, the ventilatory response will be correspondingly retarded.

The circulation time has been measured in a number of cardiac conditions, and in mitral stenosis it appears to be increased, especially in the pulmonary circuit (Tarr *et al.*, 1933; Cannon *et al.*, 1939; and Gubner *et al.*, 1939). However, the dye method (Swan and Wood, 1953) has shown normal appearance and build up times in pulmonary stenosis and in patients with left-to-right shunts, suggesting that in congenital heart disease alterations in the calibre of the pulmonary vessels serve to maintain a normal pulmonary circulation time over a wide range of flow rates. On the other hand, some congenital heart patients show a delayed ventilatory response to exercise (Davison *et al.*, 1953), and in the present series the response of the congenital heart patients to a 5 per cent mixture of carbon dioxide was rather slower than in normal subjects. It is difficult to be certain that these differences can be attributed to variations in the circulation time, since such changes in ventilation are initiated partly via higher centres of the brain, and the normal subjects were quicker to appreciate that carbon dioxide was being administered, but it is clearly impossible to state with certainty that stimuli reach the respiratory centre via the blood stream with equal rapidity in all forms of congenital heart disease.

Physical Development. The effector side of the respiratory system is not grossly impaired even in the more severe forms of congenital heart disease. Where central cyanosis is severe, particularly in cases of transposition and pulmonary atresia, general physique may be below average; there may also be moderate kyphosis or a Harrison's sulcus, and if there has been cardiac hypertrophy from an early age there may also be some prominence of the left chest wall. However, these changes were not usually very severe, and it seems unlikely that many of these patients present physical factors sufficient to affect the pattern of resting respiration or limit the response to a mild respiratory stimulus.

Discussion

It would appear from the ventilatory measurements that the resting respiratory minute volume is greater than the accepted normal value in a number of types of congenital heart disease, acyanotic as well as cyanotic. However, it is important to be certain that these are real changes, and not due merely to voluntary hyperventilation. In the present observations, care was taken to reassure the subjects and allow them to become accustomed to the use of respiratory apparatus. Objective evidence of the success of these measures is to be found in the relatively normal respiratory rate, and the absence of a correlation between the level of resting ventilation and the alveolar carbon dioxide concentration. Study of the chemical composition of the blood gives further evidence of

a genuine increase of ventilation, since there is a reduction in the carbon dioxide content of the blood, with compensatory changes in acid/base balance which tend to maintain a normal arterial carbon dioxide tension. However, it is still possible that part of the hyperventilation is of voluntary origin, and it is therefore more satisfactory to compare the different forms of congenital heart disease rather than attempt a direct comparison with healthy subjects.

In cyanotic patients, the increase in ventilation is achieved mainly by a larger tidal volume, and the respiratory rate corresponds fairly closely with that found in patients whose only physiological abnormality is an increase of right ventricular pressure. It would seem that a number of variables contribute to this increase of tidal volume, perhaps the most important being a true or relative hypercapnia of the medullary centres, brought about by the primary factors of a venous-arterial shunt and a reduced pulmonary flow. The pattern of increased respiration is probably influenced to some extent by the mechanical effects of changes in the level of pulmonary flow, but the degree of correlation between tidal volume and flow is increased by the fact that the degree of tissue hypoxia and hypercapnia is also largely dependent on the rate of pulmonary flow.

In the acyanotic patients, there is an increase primarily of respiratory rate, and it would seem that this rapid, shallow, and inefficient pattern of respiration is related largely to an increase of pulmonary flow. The mechanical basis is a matter for conjecture, but it may be postulated that the increase of flow produces an increased viscosity of the lungs (" lungenstarre " effect), and this in turn favours a shallow pattern of breathing. It is clear that in the presence of a left-to-right shunt, the acyanotic patients fail to achieve a normal pattern of respiration, although the abnormality seems mainly mechanical rather than chemical in type. On the other hand, the acyanotic patients with only an increase of right ventricular pressure show no significant abnormality of respiration, and this group therefore provides the best control with which the other patients may be compared.

In none of the types of congenital heart disease studied is the degree of hyperventilation very great, and in most instances a fairly adequate explanation can be found in changes outside the respiratory centre. It is therefore probable on the evidence of resting respiration alone that there is no large change in the sensitivity of the respiratory centre.

Summary

The pattern of resting respiration has been studied in 91 cases of congenital heart disease, and to facilitate this analysis patients have been divided into four classes: central cyanotic, peripheral cyanotic, acyanotic with increased right ventricular pressure, and acyanotic with increased pulmonary flow.

Most patients show some evidence of hyperventilation at rest. In the cyanotic classes this is due to an increase of tidal volume, rather greater in those with central cyanosis. Of the acyanotic, those with only an increase of right ventricular pressure show a normal pattern of respiration, but those with an increased pulmonary flow show some hyperventilation associated with a rapid respiratory rate. Calculation of the ventilatory equivalent shows that in most instances the hyperventilation is inefficient from the standpoint of oxygen exchange.

The chemical composition of the blood shows changes typical of a mild compensated hyperventilation. There is a decreased carbon dioxide content and alkali reserve, with relatively normal carbon dioxide tensions and *p*H values in the arterial blood.

Examination of the variables affecting the respiratory system suggests that the hyperventilation in cyanotic patients is predominantly due to a true or relative hypercapnia, while in patients with an increased pulmonary flow it is thought that an increased viscosity of the lung tissues is responsible for the shallow and inefficient pattern of respiration. Other variables, such as the level of baroreceptor discharge, the circulation time, and the physical development of the respiratory apparatus seem of relatively minor importance.

My thanks are due to Dr. Campbell for his helpful advice during the preparation of this paper, to the Department of Medical Illustration for the figures, and to Miss Scott for valued technical assistance.

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THE BLOOD FLOW IN THE RIGHT ATRIUM AND SUPERIOR VENA CAVA IN TRICUSPID INCOMPETENCE

BY

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In the course of a study of tricuspid incompetence (Müller and Shillingford, 1954) it was found that a high mean venous pressure in congestive cardiac failure was frequently associated with an abnormal right atrial pressure curve. Analysis of a series of right atrial pressure curves in normal subjects and patients with cardiac failure (Korner and Shillingford, 1954) showed in the latter group a progressive change in their form as the mean right atrial pressure rose; with moderate rises of venous pressure there was impairment of the *x* descent, and in the presence of a greater mean pressure, a positive systolic wave was found. In view of these findings we have made further studies on the blood flow in the right atrium and superior vena cava to elucidate the part played by functional tricuspid incompetence in the altered hæmodynamics of cardiac failure.

The purpose of this paper is to describe a technique for the measurement of blood flow in the atrium and superior vena cava in man, and to show the changes that occur with the development of tricuspid incompetence.

METHODS

Thirteen patients were studied; in five there was no evidence of tricuspid incompetence and in eight a tricuspid leak was diagnosed clinically and confirmed by right atrial pressure records.

A Cournand double lumen catheter, with one hole at the tip and the other at the side 10 cm. back from the first, was directed via the ante-cubital vein into the right atrium such that the end hole was two or three cm. inside the right atrium and the side hole in the superior vena cava. The catheter was connected to a sensitive differential manometer (Müller and Shillingford, 1954), the output of which was amplified by a direct current amplifier and recorded on an Elmqvist electrocardiograph. The recording system was so arranged that if the pressure were higher in the right atrium than the superior vena cava the deflection would be below the zero line, if the pressures were equal there would be no deflection, and if the pressure in the superior vena cava were higher than in the right atrium the deflection would be above the line.

The interpretation of the curves so recorded was based on experiments carried out in a heart circulation model (Fig. 1); this consisted of a rubber balloon suspended in a glass chamber (R.V.), rhythmically compressed with air from a compressor and a suitable valve mechanism. Water was pumped from this through a glass valve (P.V.) into an elastic system representing the arterial tree in which a variable resistance could be introduced by compressing a rubber segment enclosed in a glass tube (V.R.). The return flow then passed to an elastic bag (R.A.), representing the right atrium, the elastic properties of which could be altered by means of variable air pressure in a surrounding flask. This was connected to the " ventricle " via a glass valve representing the tricuspid

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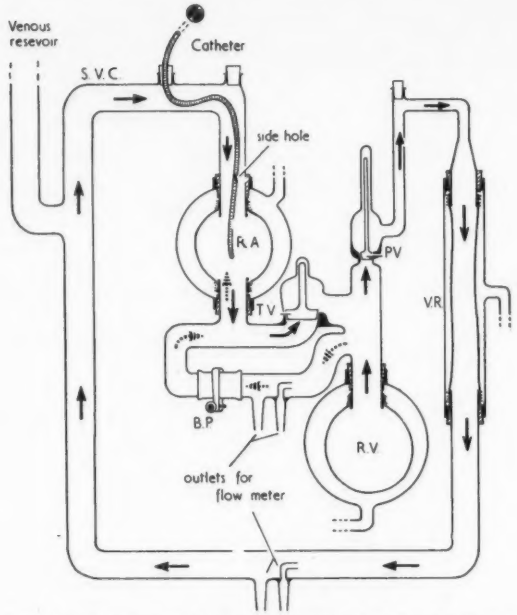

FIG. 1.—Diagram of the arrangement of the model heart used for testing the technique of measuring blood flow. R.A., " right atrium." T.V., " tricuspid valve." B.P., bye-pass of " tricuspid valve." R.V., " right ventricle." P.V., " pulmonary valve." V.R., variable resistance. S.V.C., " superior vena cava."

valve. Varying degrees of " tricuspid " leak could be introduced by means of a bye-pass tube and variable stop cock (B.P.). The amount of forward flow and regurgitation were determined by Pitot flow meters suitably placed in the circuit. The same double lumen catheter as was used in the patients was placed in the " atrium " so that the end hole was just inside the cavity and the side hole in the " superior vena cava."

EXPERIMENTAL RESULTS IN THE HEART MODEL

The relationship between the differential pressures obtained between the two catheter lumina and the known regurgitant flow followed the formula for the Pitot type of flow meter, i.e. the flow plotted against the square root of the differential pressures was linear under conditions arranged to simulate as closely as possible those found in man (Fig. 2). The sensitivity was such that a back flow as low as 4 ml. a beat could be easily detected.

The position of the catheter in the " atrium " and " superior vena cava " did not greatly affect the resultant record provided that the tip did not lie too near the orifice of the " tricuspid valve." Withdrawing the catheter so that both the end holes were inside the " superior vena cava " gave a curve of very similar pattern to that before withdrawal and with only slight changes in magnitude (Fig. 3, A and B).

The effect of altering the venous pressure in the " atrium " is shown in Fig. 3, C and D: as the pressure was raised the regurgitant stream did not rise to such a high rate of flow at the beginning of ventricular systole but tended to persist longer so that the total volume of regurgitated blood

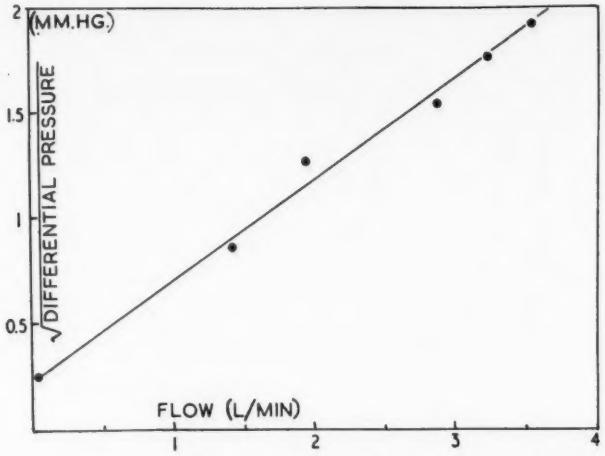

FIG. 2.—The relationship between the differential pressures recorded from the double lumen catheter and actual fluid flow as measured in the model heart.

was approximately the same. An increase in the rigidity of the system by placing a cork in the outlet of the venous reservoir to the air had a similar effect, which was more marked than the effect of increasing the venous pressure. The timing of the events in the cycle was recorded by a phonocardiographic tracing of the opening and closing of the " tricuspid " valve.

These results showed that the direction of the deflection of the curve always gave the direction of the actual flow and an indication of the amount of that flow throughout the cardiac cycle.

RESULTS IN PATIENTS

The curves obtained from our patients in all cases closely resembled those produced in the model. The normal curve (Fig. 4A) showed a small reversed flow between the right atrium and superior

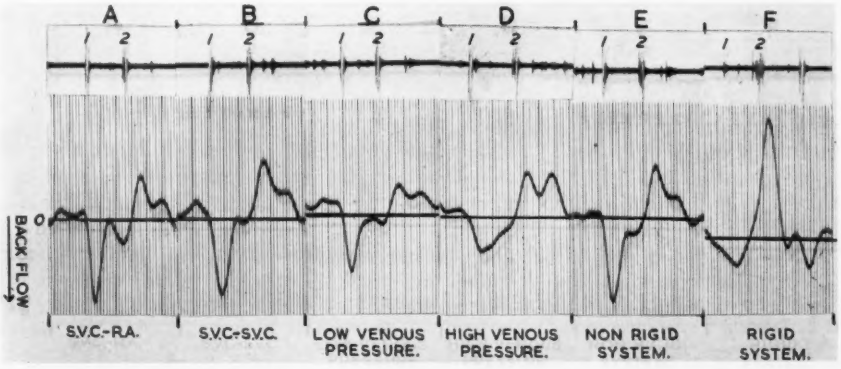

FIG. 3.—Flow patterns recorded by the double lumen catheter system in the model heart with a regurgitant stream equal to the forward output from the " right ventricle." (A) With the catheter tip in the " atrium " and side lumen in the " superior vena cava." (B) With the tip and side lumen in the " superior vena cava." (C) and (D) The effect of raising the venous pressure. (E) and (F) The effect of increasing the rigidity of the atrium and venous system.

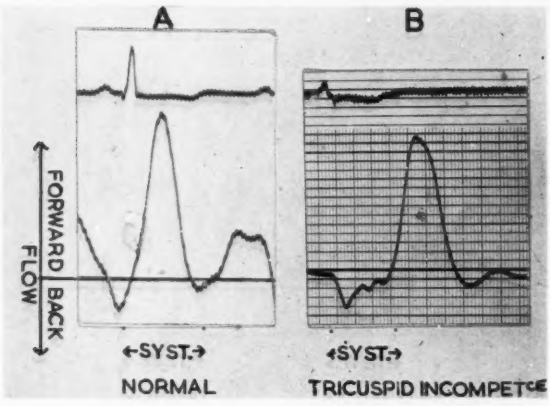

FIG. 4.—The blood flow between the superior vena cava and right atrium in a normal subject (A) and one with tricuspid incompetence and high venous pressure (B).

vena cava during atrial systole. This rapidly gave way to a forward flow which reached its maximum in mid-ventricular systole and during descent of the base of the heart. At the end of systole the flow stopped and in some cases was slightly reversed during return of the base of the heart; the forward flow restarted early in diastole and continued until atrial systole. Most of the forward flow from the superior vena cava to the right atrium occurred during ventricular systole and descent of the base of the heart. A similar pattern was obtained between the inferior vena cava and right atrium.

In tricuspid insufficiency the normal pattern was greatly modified; as the tricuspid leak increased the forward flow during descent of the base decreased and in most cases was replaced by a reversed flow; where the venous pressure was not high and the venous system not tense this occurred for the most part early in systole (Fig. 5B), but in the presence of a higher venous pressure and a tense atrium the reversed flow tended to be more evenly distributed throughout systole (Fig. 4B). All the forward flow from the superior vena cava to the right atrium in these cases occurred during diastole.

The effect of exercise in increasing the amount of tricuspid leak is well shown in Fig. 5. The patient had chronic rheumatic heart disease with mitral stenosis and early cardiac failure. At rest there was a slight tricuspid leak with some impairment of forward flow in systole and a mean venous pressure of 10 mm. Hg. Two minutes exercise raised the mean venous pressure to 15 mm. and produced a considerable increase in the regurgitant stream during ventricular systole.

DISCUSSION

The experiments with the double lumen catheter in the model showed that the catheter-manometer system worked as a Pitot flow meter and gave a reliable indication of the presence of forward or reversed flow. The effect of changing the position of the catheter in the atrium and superior vena cava was surprisingly small; in man also the form of differential pressure curves did not vary greatly on withdrawal of the distal hole into the superior vena cava. A quantitative approach was possible in the model (Fig. 2) but owing to the presence of the inferior vena cava and other variable factors was not attempted in man.

The phasic variations in flow patterns in man closely resembled the curves obtained by Brecher (1954) in dogs by means of a bristle flow-meter. Normally the greater part of the forward flow of

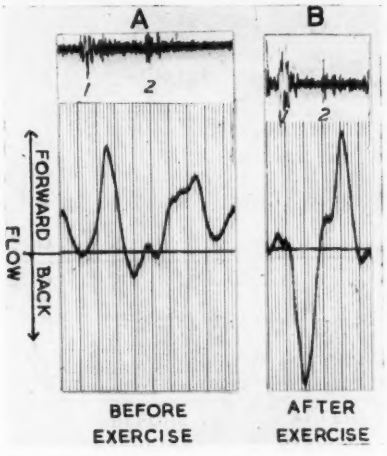

FIG. 5.—The effect of exercise on the degree of tricuspid incompetence in a patient with mitral stenosis and early cardiac failure.

blood from the great veins to the atrium occurs during ventricular systole and descent of the base of the heart; this forward flow correlates with the drop in atrial pressure (*x* descent) found in this part of the cardiac cycle. The blood flow stops, or even becomes momentarily reversed, at the time of the return of the base of the heart and starts again during diastole, but at a lower level than in systole. The effect of atrial contraction, although visible on the curves, is slight.

In tricuspid incompetence the normal phasic flow is greatly altered; where the leak is small the forward flow in systole is reduced by the regurgitant stream but the overall flow is still from the great veins to the atrium; a greater part of the forward flow then occurs in diastole. Factors that normally increase tricuspid incompetence in borderline cases may change one type of curve into the other. This was well shown in Fig. 5 where the patient on being exercised developed the typical flow pattern of gross tricuspid incompetence as well as a rise in venous pressure.

The effects of varying venous pressure and volume elasticity coefficient could easily be separated on the circulation model and the tracings obtained closely simulated curves made from patients in a variety of conditions. With a low venous pressure and a normal volume elasticity coefficient the backflow was greater and occurred earlier in systole than when the venous pressure was raised and the volume elasticity coefficient of the system increased, other factors remaining constant. A rising level of the venous pressure and diminished distensibility of the atrium tended to limit the amount of blood regurgitated in systole; the volume of backflow in turn affected the level of the mean venous pressure. An analysis of our curves in cases of severe tricuspid incompetence suggests that in many cases the backflow may equal or even exceed the forward cardiac output (Fig. 5B).

SUMMARY

A technique for recording the instantaneous changes in the blood flow from the superior vena cava to right atrium is described. In a model it permits of a good quantitative assessment of the rate of flow.

The blood flow in the superior vena cava and right atrium is recorded in patients with and without tricuspid incompetence. Normally the greater part of the forward flow from the superior vena cava

to the right atrium takes place during ventricular systole and the descent of the base of the heart. In gross tricuspid incompetence the forward flow mainly occurs in diastole. With smaller degrees of tricuspid leak some forward flow may still occur at the end of systole.

The volume of regurgitated blood is closely related to the volume elasticity function of the right atrium and venous system.

In some patients with heart failure and functional tricuspid incompetence the amount of back-flow may equal or exceed the forward cardiac output.

We should like to thank Professor McMichael for his continued help and advice and Dr. Korner for his valuable assistance.

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A PHOTOMETRIC METHOD FOR ESTIMATING THE OXYGEN SATURATION OF SMALL BLOOD SAMPLES

BY

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Since Kramer (1933) investigated the optical properties of hæmoglobin/oxyhæmoglobin solutions, many methods have been proposed for the photometric estimation of the oxygen saturation of blood. A new method can only be advocated if it offers economy of apparatus or reagents, greater ease of performance, or the elimination of sources of error. It is upon these grounds that the following method is proposed for consideration.

METHOD

(1) *Colorimeter and Cuvettes.* Any simple photoelectric colorimeter that employs small cylindrical cuvettes of about 0·5/0·6 cm. internal diameter could be used. We have used the "EEL" portable colorimeter with the " EEL " Filter No. 205 (6500° A).

As will be explained, hæmolysed but minimally diluted blood is used for the estimation and if the cuvette were filled with this solution, its optical density would be too great for evaluation in a simple colorimeter. The optical thickness of the cylindrical cuvette (" EEL " No. 305) is therefore reduced by inserting a glass rod of 5·32/5·40 mm. maximum diameter and with ovality of not more than 0·15 mm.

The rod is located centrally in the cuvette by (*a*) grinding its lower end flat, and (*b*) wrapping around its upper end waterproof self-adhesive tape to form a sleeve which fits snugly into the cuvette (Fig. 1).

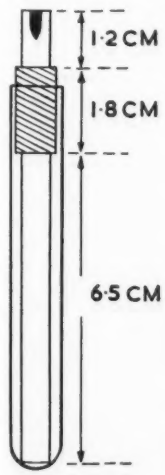

FIG. 1.—Rod for reducing optical thickness of cuvette.

We obtained the glass rod by purchasing Pyrex rod of nominal 5–6 mm. diameter. From the delivery, a considerable quantity of suitable rod was selected, using a micrometer. After the rods had been cut and prepared they were indexed as follows : About ½ ml. of a light blue solution (1:80 dilution of Waterman's Royal Blue Ink) is put into one of the cuvettes and a rod inserted. The rod is slowly rotated while watching the meter. The meter reading varies, but over a portion of the circle considerable angular rotation of the rod produces only small changes in the meter reading. With the rod in this position, a mark is made upon it to line up with the locating mark on the cuvette tube. Thereafter, the rod is always lined up in this way whenever it is used. The purpose of this adjustment is to make sure that errors in the alignment of the rod will have a minimal effect upon the accuracy of readings.

A final check upon the satisfactory size of the glass rod should be made with blood. A fully reduced hæmolyzed specimen of blood of normal hæmoglobin concentration is prepared as described in a later paragraph. This is put into the cuvette and the rod inserted. The meter reading should lie between 84 and 91 on the logarithmic scale. The purpose of this selection is to ensure that blood containing up to 110 per cent of hæmoglobin can conveniently be estimated with minimal dilution.

It is convenient to provide 3 rods for each set of 12 tubes, one tube and rod are kept filled with distilled water for zero setting, one rod is in use, and one is held as a spare.

The cuvette tubes must fit snugly and firmly in the holder of the colorimeter. To achieve this, some form of spring clip has to be fashioned to press the cuvette against one side of the holder. The holder for the "EEL" colorimeter is an ebonite

rod drilled axially to accept the cuvette tube and with slots through which the light passes. Regarding the top of this holder as a clock face and the light path as passing through 6 to 12 o'clock, we drilled two small holes downwards into the holder at 3 and 9 o'clock. Into these holes were dropped the limbs of an inverted U of spring wire so that the centre of the U stood about ½ cm. above the top of the holder. The U must be thrust a little aside when the tube is inserted and it then holds the tube firmly.

(2) *Hæmolyzing Syringe.* A 1-ml. long tuberculin syringe is used and it contains a stainless steel ball about 5/32 in. in diameter. A horseshoe pocket magnet (Eclipse) is used to move the ball around within the syringe in order to mix its contents quickly.

Reagents. (1) A synthetic detergent solution is used to secure hæmolysis. Probably many detergents would serve but we have employed undiluted " Lissapol."

(2) Sodium hydrosulphide is used to secure complete reduction of the hæmoglobin solution. Hydrosulphide seems to be an impermanent substance and it should be stored either in sealed ampoules or in small, well-filled and well-closed tubes.

(3) Heparin has been used to prevent coagulation of the blood sample which is stored, anærobically, in a capped syringe.

Procedure. (1) Draw into the hæmolyzing syringe a little detergent solution, expel all air bubbles and push the plunger down until it is stopped by the stainless steel ball. The dead space of the syringe and its hub are now filled with detergent.

(2) Ensure that the blood sample is well mixed, expel the blood held in the hub of the sample syringe, and join the sample syringe to the hæmolyzing syringe with a very short piece of elastic tubing.

(3) Drive blood gently into the hæmolyzing syringe until the plunger stands at the 0·8-ml. mark.

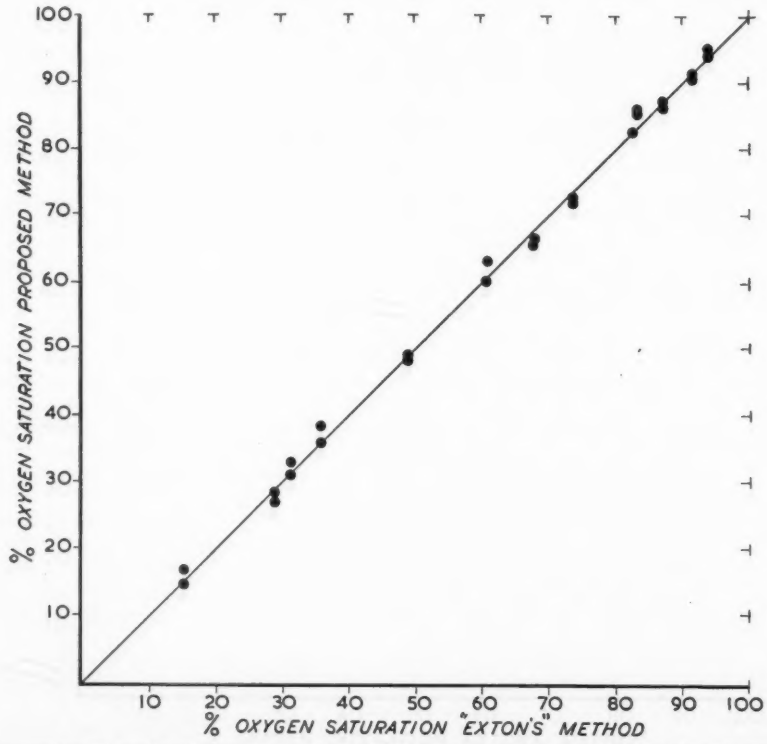

FIG. 2.—Comparison of results of oxygen saturation with simultaneous determinations by Exton's method.

(4) Disconnect the hæmolyzing syringe and, with the magnet, move the steel ball briskly for 15 to 30 seconds to secure hæmolysis. The hæmoglobin solution will become quite clear.

(5) Expel 0·1 ml. from the hæmolyzing syringe to waste in order to clear the hub of unhæmolyzed blood, and attach a blunted needle 10 cm. long.

(6) Expel the hæmolyzed blood gently into the cuvette holding the tip of the needle on the bottom of the cuvette.

(7) Set the instrument to zero using a similar rod and cuvette containing distilled water. Place the sample cuvette and rod into the instrument and take a reading *Rb*.

(8) Withdraw the glass rod from the cuvette and wipe it clean. Place a finger over the top of the cuvette and shake it in a horizontal position for one minute. This suffices fully to oxygenate this small quantity of hæmoglobin solution.

(9) Restore the glass rod and take a second reading in the colorimeter *Ro*.

(10) Spread a little hydrosulphide in a thin but continuous layer on a tile. Remove the glass rod and touch its moist flat end upon the hydrosulphide so that crystals adhere to the flat surface. Return the rod to the cuvette and work it up and down for 15 seconds. This suffices fully to reduce the hæmoglobin solution.

(11) Wait half a minute to allow any bubbles to come to the surface, and return the cuvette to the colorimeter. Take a third reading *Rh*. If the blood sample contains more than 110 per cent hæmoglobin, it must be diluted slightly. This is accomplished by completing step (1) and then drawing boiled cooled distilled water into the syringe to the 0·3-ml. mark. Thereafter, proceed as described. This small extra dilution serves to bring within the operating range of the colorimeter blood containing up to 150–160 per cent of normal hæmoglobin.

Calculations

The colorimeter we employ has a logarithmic scale so that readings may be taken directly from it. The calculation is then as follows:

$$\text{Percentage oxygen saturation} = 100 \times \frac{Rh - Rb}{Rh - Ro}$$

Alternatively, the mechanical nomograph described in the Appendix may be used (Fig. 3).

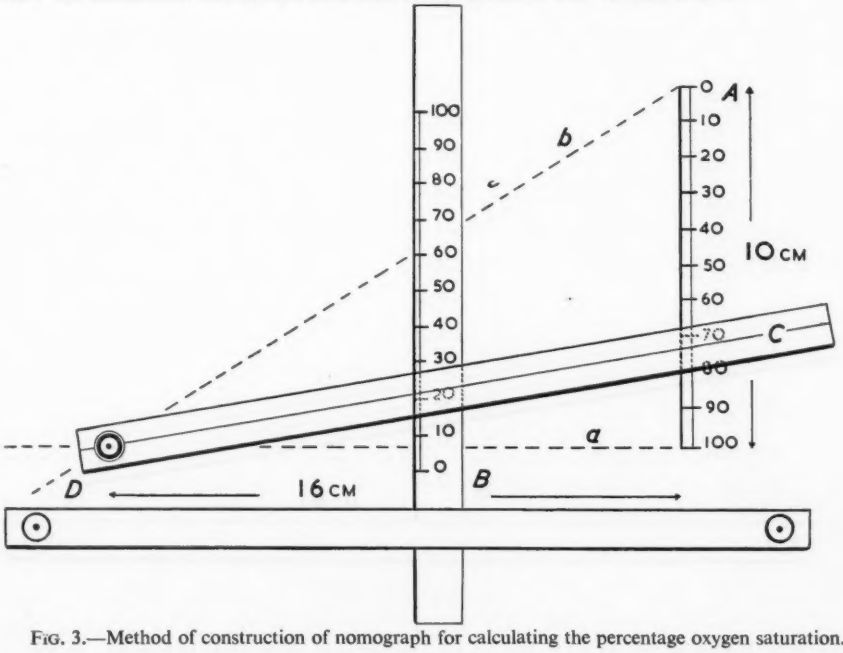

Fig. 3.—Method of construction of nomograph for calculating the percentage oxygen saturation.

Discussion

We have examined the accuracy of the method by comparing its results with simultaneous determinations of oxygen saturation of blood using Exton's method (1945), slightly modified for convenient operation (Pask, 1953). The results of the comparison are presented in Fig. 2.

Blood samples were drawn from the veins of five subjects after varying periods of occlusion and at various temperatures. There was thus considerable variation both in hæmoglobin and oxygen content.

The rather good agreement of figures for low oxygen saturations is noticeable since this is not always achieved by photometric methods. The fact that the line drawn through most experimental points also passes through 0 and 100 per cent on both scales, is additional confirmation that the two methods agree in the low range as well as at higher percentage saturations.

The advantage of this method seem to us to be that it is easy and rapid to perform. An estimation can be completed in four minutes. The apparatus needed is not expensive and quite small blood samples can be used.

The blood is only slightly diluted, even when high hæmoglobin concentrations are encountered. The effect on the oxygen content of the added diluent is therefore very small and no attempt need be made to correct for the change in saturation that might result from a considerable dilution such as is used in some other methods.

The three readings necessary for the construction of a calibration line for a particular sample, are all obtained in the same cuvette on the same sample within a short space of time. Thus, no assumptions need be made about the slope of this line.

In common with all methods employing hæmolysis, variations in corpuscle size and shape do not affect the results nor is sedimentation a source of difficulty.

We are grateful to Evans Electroselenium Ltd., of Harlow, for their assistance in developing this method. Readers who wish to purchase suitable colorimeter tubes and glass rods should make enquiry of this firm.

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Exton, W. G., Schattner, F., Korman, S., and Rose, A. R. (1945). *J. Lab. Clin. Med.*, **30**, 84.
Kramer, K. (1933). *Klin. Wchnschr.*, **12**, 1875.
Pask, E. A. (1953). *Brit. J. Anæsth.*, **25**, 297.

Appendix

A Simple Nomograph. A piece of plywood has drawn on it a scale " A " graduated 0–100 per cent. From each end of this scale lines are drawn which meet at " D," the centre for a movable perspex cursor " C." Scale " B " is the same length as scale " A " but can be moved laterally and vertically (Fig. 3).

Operation. Scale " B " is adjusted so that while it is parallel to scale " A," *Ro* lies on line (a) while at the same time *Rh* lies on line (b). The cursor line is set to *Rb* on scale " B " when the percentage saturation is read from the cursor line on scale " A."

SOME VARIATIONS IN THE SHAPE OF THE PRESSURE CURVE IN THE HUMAN RIGHT VENTRICLE

BY

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The curves of normal intraventricular pressure have been the subject of many studies in animals. Wiggers in 1928 gave what is now the standard description and explanation of these and summarized the extensive literature up to that date.

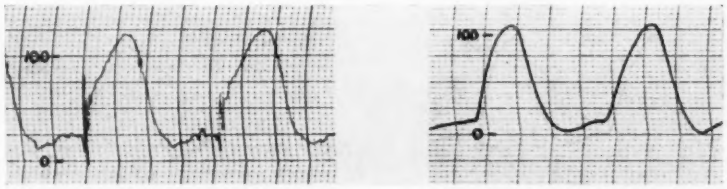
The purpose of this investigation is to study the curve of right ventricular pressure in man and how it may become modified under abnormal conditions. In particular, a comparison has been made between the right ventricular tracings in pulmonary hypertension and pulmonary stenosis—the two common situations in which right ventricular pressure is raised.

Material and Methods

Pressure tracings have been made during the course of routine cardiac catheterization. With one exception, therefore, the subjects have all had some cardiovascular abnormality. Adequate records have been available in 43 patients. Thirty-eight had intact ventricular septa, and these comprise the main study. They have been divided into three groups; those with normal pulmonary artery pressure (11); those with pulmonary hypertension (15); and those with pulmonary stenosis (12). In addition there have been three patients with an isolated ventricular septal defect, and two with Eisenmenger's complex.

Pressure readings have been made with a capacitance manometer using the apparatus devised by Bareham (1954). Tracings from the pulmonary artery have been taken within a short time of those from the right ventricle, but there have been no simultaneous recordings of pressure. Cardiograms have been recorded simultaneously with the pressure tracings, and, where pulmonary artery pressure curves have been drawn on top of those from the right ventricle, the time relationship of the two curves has been arrived at by superimposing the QRS complexes of the cardiogram.

Distortion of the tracings may be due to intermittent occlusion of the tip of the catheter by pulmonary (Lagerlöf and Werkö, 1949) or tricuspid (Lenègre and Maurice, 1946) valves, or by the ventricular wall itself. It may also arise owing to excessive damping when the catheter contains blood, and this is particularly found towards the end of the examination when, following the taking of a number of blood samples, a fine deposit of coagulum has presumably formed within the lumen of the catheter (Fig. 1). All tracings showing such distortions have been excluded.



A B

FIG. 1.—Right ventricular tracings from the same case to show the effect of excessive damping due to clogging of the catheter. (A) Catheter lumen free, (B) Catheter clogged. In this and all subsequent figures, the manometric scale refers to mm. Hg.

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Pressures have been measured from the level of the table on which the patient was lying. Different authors have used different points of reference for their level of zero, and some adjustment has to be made before their figures may be compared (Holling and Zak, 1950). When converted in this way to measurements from the level of the table, the upper limit of normal right ventricular systolic pressure found by various authors is 40 mm. Hg (Bloomfield *et al.*, 1946 ; Dexter *et al.*, 1947 ; Dexter *et al.*, 1950 ; Lagerlöf and Werkö, 1948). In the " normal " group of this study the right ventricular systolic pressure has been below 40 mm. Hg and in the group with pulmonary hypertension it has been above 50 mm. Hg.

Throughout this discussion, the term " systole " has been used to mean the whole of the major wave of the ventricular pulse and thus includes isometric contraction, ejection, and isometric relaxation.

RESULTS

Normal Right Ventricular Pressure. All except one of these cases have had some cardiac abnormality. Nevertheless, it has been thought justifiable to assume the function of the right ventricle to be normal where the pressure in the pulmonary artery is normal and the ventricular septum intact, whatever abnormalities might exist elsewhere in the heart.

Fig. 2 shows tracings from two such cases. Right ventricular systole starts with a sudden rise in pressure corresponding to the isometric phase of contraction. After this, the tracing alters its direction and follows the shape of the curve of pressure in the pulmonary artery. This, therefore, is the ejection phase. It occupies most of ventricular systole. Most often the tracing during this phase rises to a low summit very quickly and then declines gradually to the point of closure of the pulmonary valves. This, however, is not invariable. In one case it rose gradually to reach a gentle summit near its end, and in one case it was quite level. In another it was seen to vary according to the changing intrathoracic pressures during the respiratory

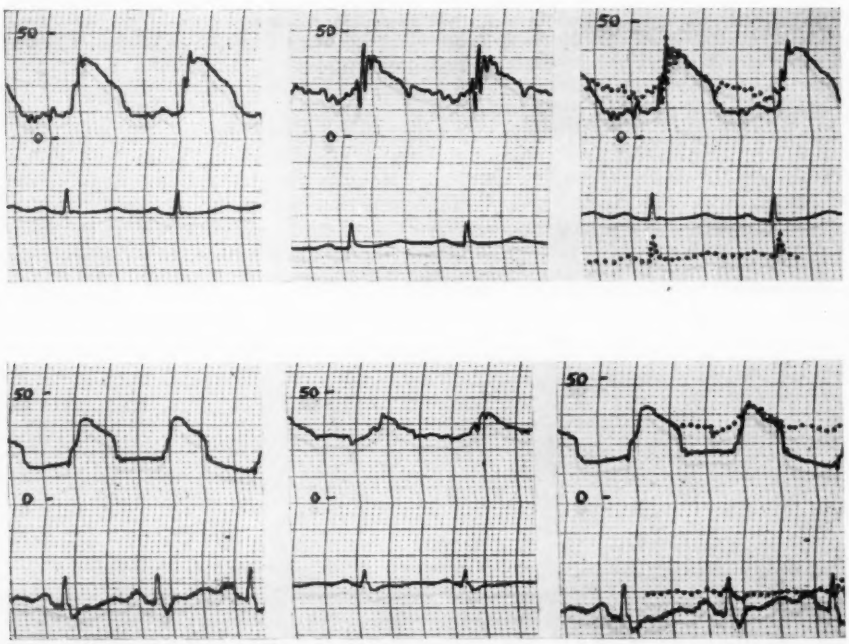


FIG. 2.—Tracings from two patients with normal right heart pressures. The left-hand column shows the right ventricular tracings ; the middle column shows the pulmonary artery tracing ; on the right hand the two are superimposed.

cycle (Fig. 3). The third phase of the pulse wave is a sudden decline of pressure corresponding to isometric relaxation. This occurs approximately at the incisura of the pressure curve in the pulmonary artery.

The initial rise of the ejection phase may be quite steep so that it appears to be a continuation of the isometric contraction phase, and the true point of demarcation between the two phases does not become apparent until the tracing from the pulmonary artery is superimposed. Although, therefore, in these cases the right ventricular curve is " squared off " into three distinct divisions, these do not strictly correspond with the three physiological phases of systole. Thus the upstroke consists of isometric contraction plus the beginning of ejection, the " plateau " is the last part of ejection, and the down stroke is isometric relaxation.

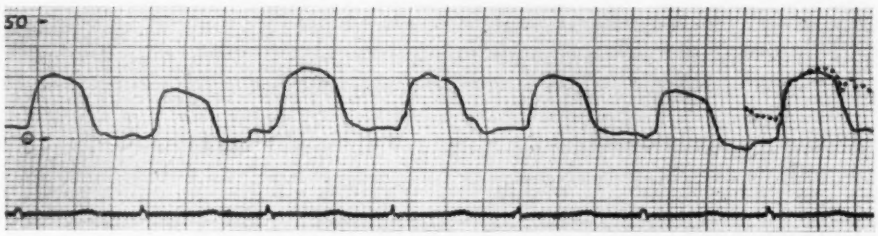


FIG. 3.—Right ventricular tracings from a child of two years with an atrial septal defect. The gross undulations in intrathoracic pressure due to respiration affect the shape of the ejection phase.

Pulmonary Hypertension. Seven of these patients were suffering from mitral stenosis. Four had " primary " pulmonary hypertension, two atrial septal defect, one pulmonary fibrosis, and one patent ductus arteriosus. The general shape of the recording from the right ventricle was the same in all these patients, no matter what the origin of the high pressure in the pulmonary artery.

As in the normals, the pressure tracing during ventricular systole comprises three distinct phases ; isometric contraction, ejection, and isometric relaxation (Fig. 4). The abrupt rise and fall of the first and third phases is unchanged. The deflections are, however, naturally of greater amplitude, and the fall of pressure during isometric relaxation is increased disproportionately. Once again, the right ventricular curve in the ejection phase is seen to correspond with that of the pulmonary artery. But, instead of a quick rise and gradual fall, this part of the curve rises steadily and the summit is reached only towards the end of ejection. The more severe the pulmonary hypertension, the steeper is this rise. The descent from the summit usually passes imperceptibly into the phase of isometric relaxation. Hence, again, the three apparent divisions of the pulse wave usually do not correspond with the physiological phases of systole. In this case, however, the upstroke represents isometric contraction and the " plateau " the first part of the ejection, while the downstroke comprises the last part of ejection plus isometric relaxation.

Pulmonary Stenosis. Twelve cases were studied. Ten of these were of the valvular type and two infundibular. In no case was there any evidence of a ventricular septal defect. In two cases an atrial septal defect was shown.

Where the stenosis is valvular, the shape of the right ventricular systolic pulse is quite different from that in either of the two preceding groups (Fig. 5). No distinct divisions of systole are apparent and the tracing becomes a simple hump with its summit in mid-systole. This pattern was consistently found and held good even for the mildest cases with systolic pressures in the region of 50 mm. Hg. The pulse wave in this way sometimes approaches the shape of an isosceles triangle. A small notch on the upstroke may correspond with the first sound.

There is great similarity between the tracings from the main chamber of the right ventricle in the two patients with infundibular stenosis. The pulse wave, however, differs from that found where the obstruction is at the valve. Its shape approximates to that observed in patients with pulmonary hypertension (Fig. 6). There is an abrupt upstroke followed by a gently rising " plateau " which reaches its summit towards the end of systole and then descends rapidly towards the base line.

Patients with Ventricular Septal Defects. Adequate studies of patients with ventricular septal defects have been limited and will be given only brief consideration here. Three patients had an isolated ventricular septal defect and a large shunt of the type described by Wood (1950) and Joly *et al.* (1951). In all three, there was great similarity in the shape of the right ventricular pulse wave which

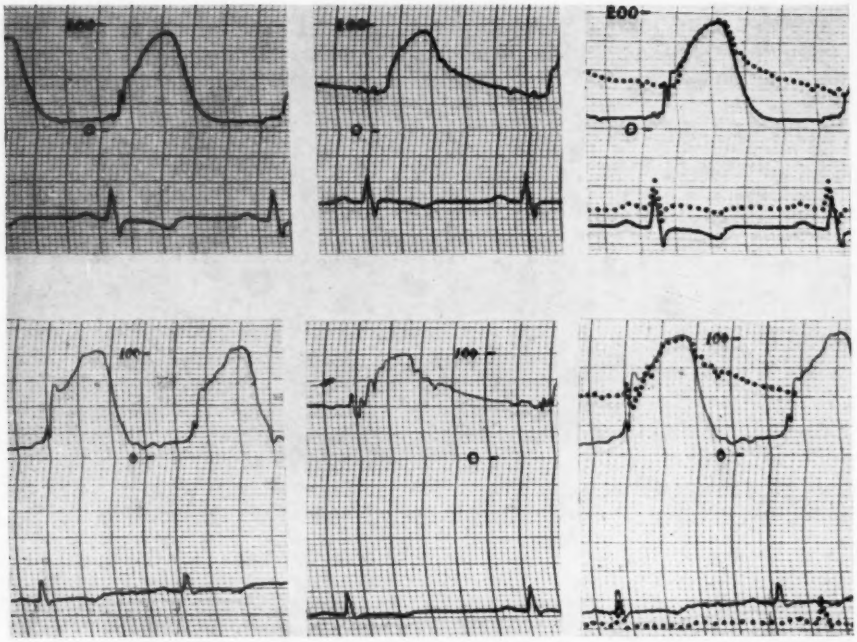


FIG. 4.—Tracings from two patients with pulmonary hypertension. The left-hand column shows the right ventricular tracings ; the middle column shows the pulmonary artery tracing ; and on the right hand the two are superimposed.

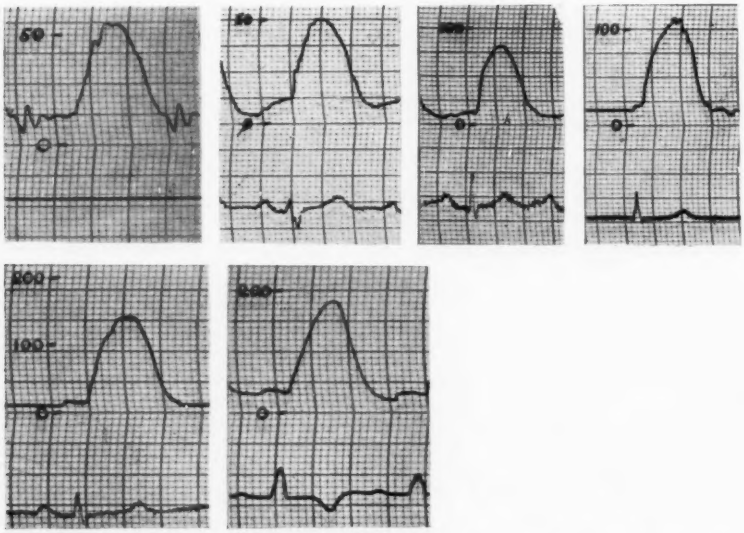
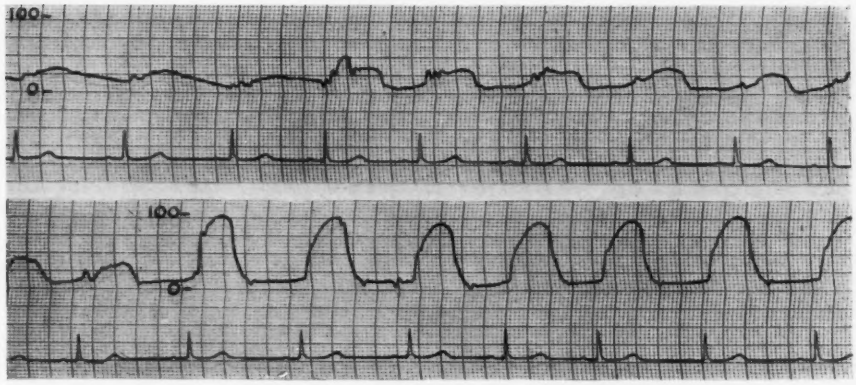


FIG. 5.—Right ventricular recordings from patients with pulmonary valvular stenosis of varying severity.



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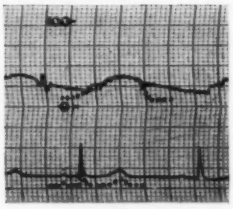

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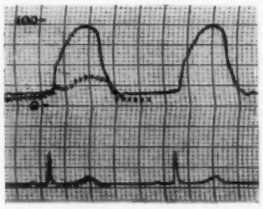

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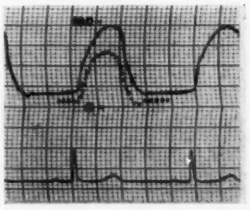
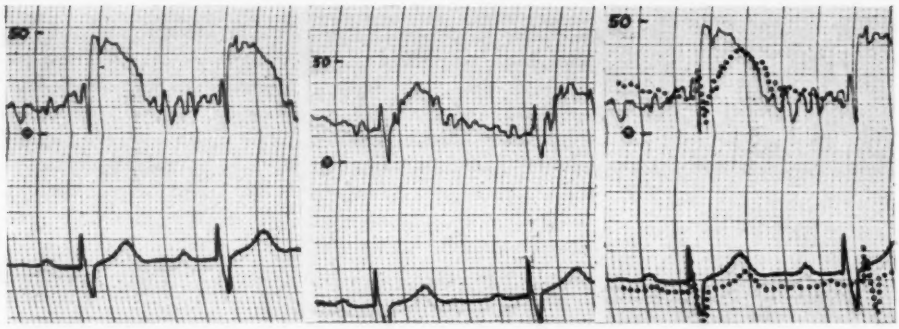


D

FIG. 6.—From a patient with isolated pulmonary infundibular stenosis. (A) Withdrawal of catheter from the pulmonary artery through the infundibulum to the right ventricle ; (B) Pulmonary artery tracing with infundibular tracing superimposed ; (C) Right ventricular tracing with infundibular tracing superimposed ; (D) Right ventricular tracing. The dotted line here shows the curve that results when the infundibular tracing is subtracted from that in the right ventricle.

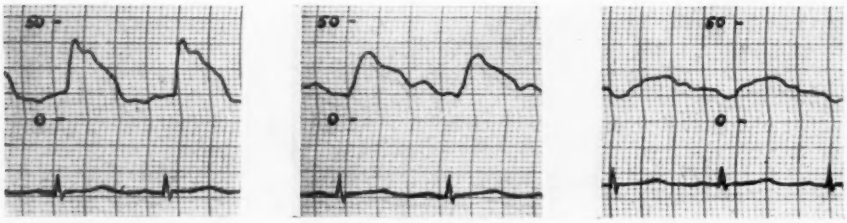
rose suddenly to an unusually high peak at the beginning of systole (Fig. 7). This peak, which thus initiated the phase of ejection, was not recorded in the tracings taken from the right or left main branches of the pulmonary arteries. When, therefore, the pulse wave in these vessels was superimposed upon that from the right ventricle, it was seen that, during the early part of ejection, the ventricular pressure was considerably the higher of the two (Fig. 7). Thereafter, the right ventricular pressure fell to join the curve of pressure in the pulmonary artery branch in the last half of the ejection phase. The shape of the tracing from the main trunk of the pulmonary artery was found to vary from case to case. In one patient, no recording was available from this site. In another, the tracing from the main trunk corresponded with that from the left branch. In the third, the tracing from the main trunk differed from that in the branches and corresponded with the recording from the right ventricle throughout the phase of ejection (Fig. 8). Thus the change in shape of the pulse wave during this phase did not necessarily occur at the level of the pulmonary valve and could take place further downstream in the pulmonary artery.

Two patients were thought to have Eisenmenger's complex. In both of these, high right ventricular systolic pressures were found and the systolic pulse consisted of three divisions as in the patients with pulmonary hypertension. In one patient the pressure in the pulmonary artery was recorded and appeared to correspond with the right ventricular curve during the ejection phase. In the other patient the catheter passed into the aorta where, again, the curve of the ejection phase was identical with that in the right ventricle (Fig. 9).



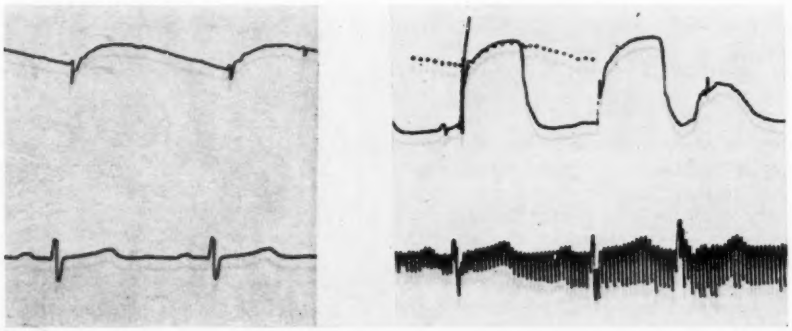
A B C

FIG. 7.—Recordings from a patient with a ventricular septal defect. (A) Right ventricular tracing; (B) Left pulmonary artery tracing; (C) Superimposed tracings.



A B C

FIG. 8.—From a child with ventricular septal defect. (A) Right ventricle; (B) Main pulmonary artery; (C) Left pulmonary artery.



A B

FIG. 9.—From a patient thought to have Eisenmenger's complex. (A) Aorta; (B) Right ventricle with aortic tracing superimposed. An "ineffective" ventricular premature beat is shown in the right ventricular tracing. The ejection phase of the tracings has probably been artificially flattened by limitation of excursion of the recording pens.

Discussion

The interpolation of a cardiac catheter between the manometer and the origin of the pulse wave seriously interferes with the accuracy of the record. If, moreover, one adds to the inadequacies of the recording system the occurrence of artefacts in the tracings due to movements of the catheter at each heart beat, the distortion of the pulse wave may well be considerable. With these considerations in mind, therefore, the analysis of the pressure curves has been restricted entirely to the grosser changes in shape. In particular, no attempt has been made to analyse the tracings during diastole when the variations of pressure are less obvious and more certainly obscured by the inadequacies of the recording technique. Since, within these limits, clearly defined differences of contour have been found between the three main groups and since these differences have been constantly observed, it is thought that they must have a meaning. Indeed, if it be said that the peculiar shapes of the curves are due solely to " artefacts," it still has to be explained how, with a uniform technique, those artefacts vary so consistently between the three groups of patients.

Wiggers (1928) found that the curve of pressure most frequently recorded in the ventricles of animals was " characterised by a comparatively smooth contour and a rounded, arched summit." The shape of curve usually recorded in the patients with normal pulmonary valves in this series corresponds to a pattern that he found less commonly in animals. However, in manometric tracings taken during cardiac catheterization of the right ventricle in human subjects (Bloomfield *et al.*, 1946; Lenègre and Maurice, 1946; Sicot *et al.*, 1951) the shape of the curves in general corresponded to that described here. Often it is not possible to evaluate the shape of published pulse tracings where the scale of deflection is disproportionately large compared with the speed of the paper.

Wiggers (1927, 1928) has described the genesis of the pressure curve of ventricular contraction. Fundamentally it is due to the summation of a large number of minute contractions. If the semilunar valves were completely occluded one would therefore imagine that the resulting systolic curve in the ventricle would be a simple smooth hump such as is found in the isometric contraction of skeletal muscle, and this is in fact what is recorded during " ineffective " premature beats when the contraction of the ventricle is too feeble to open the valve (Wiggers, 1928) (Fig. 9 and 10). In a normal beat, this dome-shaped curve is modified by the opening and closing of the semilunar valves so that in the ejection phase the ventricle is no longer acting isometrically (Fig. 11). During this phase the right ventricle and pulmonary artery become a continuous chamber so that their curves of pressure are nearly identical. The shape of the curve during this part of ventricular contraction depends entirely upon the ratio between filling and emptying of the pulmonary arterial tree. Thus the pressure rises while the volume ejected by the right ventricle exceeds that which drains into the pulmonary capillaries.

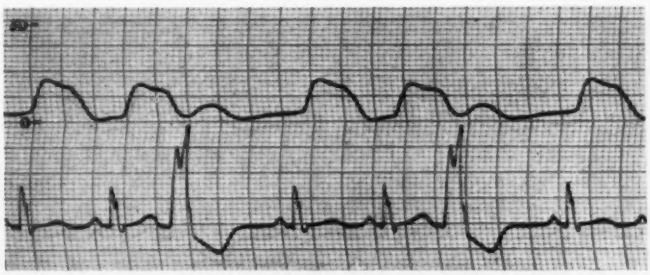


Fig. 10.—" Ineffective " ventricular premature beats. Tracings from the right ventricle of a child, aged eighteen months, with cardiomegaly of unknown ætiology.

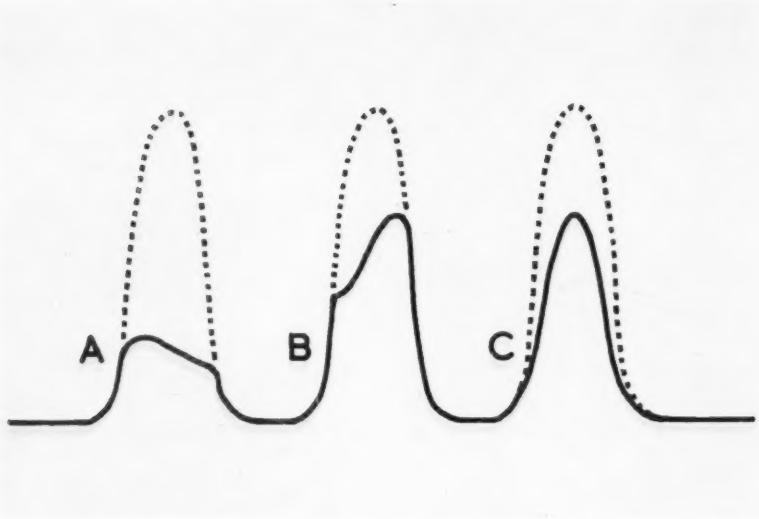


FIG. 11.—Diagram to show how the ideal isometric contraction curve of the right ventricle (represented by a dotted line) is modified by the presence of the pulmonary valves and by pulmonary stenosis. (A) Normal conditions; (B) Pulmonary hypertension; (C) Pulmonary stenosis.

Under normal conditions, pulmonary vascular resistance is low. This has a two-fold effect on the pressure curve of the right ventricle. In the first place it means that the pulmonary diastolic pressure is low and thus the isometric contraction phase of the right ventricle is of limited height. Secondly, it means that the rise in pulmonary artery pressure which follows the sudden rush of blood through the valve is rapidly high enough to cause pulmonary drainage to equal or exceed ventricular ejection. Thus, after a brief initial rise, the main slope of the ejection phase is usually slightly downward.

Conversely, when pulmonary vascular resistance is increased, the pulmonary diastolic pressure is high, so that the deflection of the isometric contraction phase of the right ventricular pulse is of greater amplitude. After the pulmonary valve has opened, the increased pulmonary vascular resistance impedes drainage from the pulmonary artery. Thus ventricular ejection comes to exceed pulmonary drainage for most of the ejection phase and the pressure mounts steadily in the right ventricle and pulmonary artery. As this phase continues, contraction gradually gives place to relaxation in the right ventricle so that the curve flattens to a summit and falls a little just prior to the closure of the pulmonary valve. The main slope of the ejection phase is therefore upward, and the summit comes towards the end, whereas in the normal group there is usually an early summit of low amplitude followed by a gradual slope downwards.

Wherever the pulmonary valve is normal, therefore, its opening and closing will cause sudden variations in the resistance to outflow of blood from the right ventricle and thus give rise to the angulations seen on the pressure tracings. When the valve is stenosed, however, the resistance to outflow from the right ventricle is constituted almost entirely by its rigid orifice. Pulmonary vascular resistance is low and can play only a negligible role since the pulse wave in the pulmonary artery becomes meagre and sometimes hardly distinguishable. Thus the resistance to outflow from the ventricle remains virtually constant throughout systole and the clear-cut divisions of the normal ventricular pulse wave are lost. The result is a smooth hump with its apex roughly central (Fig. 11). Such curves are shown by Mannheimer (1949) and Soulié *et al.* (1952). In most of

the published tracings, however, the amplitude of the deflection is disproportionately great in relation to the speed of the recording paper so that a qualitative evaluation of the curves is difficult.

It is less easy to account for the type of curve found in the two cases of pulmonary infundibular stenosis. Clearly there is some variation in the resistance to the outflow of blood from the right ventricle. Where the stenosis is at the pulmonary valve this cannot occur, for the meatus is set in a diaphragm of rigid fibrous tissue. Here, however, the channel through the infundibulum is usually surrounded by muscle and it may be that it varies in calibre during contraction and relaxation of the heart. Alternatively, if the pulmonary valve is functioning normally, its opening and closing will cause wider variations of the pressure in the infundibulum. In this way a more pronounced and angular pulse wave will be formed in the infundibular chamber and this will be superimposed upon the curve of pressure in the main right ventricular chamber.

In one of the patients with infundibular stenosis the manometric tracings lend some support to this view (Fig. 6), although the accuracy of the recordings in the infundibulum must be more than ever doubtful. In this patient it seems likely that the pulmonary valve was functioning normally. It does not appear to be stenosed since the systolic pressure was found to average 14 mm. Hg equally in pulmonary artery and infundibulum. Moreover, the cusps seem to close efficiently, for the infundibular tracing leaves the pulmonary artery tracing abruptly in the vicinity of the second sound and rises to meet it again at the beginning of systole. In virtue of this, the pulse wave in the infundibular cavity is of sufficient dimensions to have a significant effect on the emptying pressures of the main right ventricular chamber. Fig. 6D shows that, if infundibular pressure is subtracted from right ventricular pressure from point to point throughout the cardiac cycle, the curve obtained is in fact of the type seen in pulmonary valvular stenosis. In other words, the right ventricular pulse wave due to the infundibular stenosis alone would be a smooth hump, but on top of this have to be added the variations of pressure in the infundibulum consequent on the presence of a functioning pulmonary valve. It is these variations that give the pulse wave its particular shape.

The observations made on patients with isolated ventricular septal defects permit of only tentative conclusions. Presumably the inter-ventricular communication allows the more vigorous beat of the left ventricle to be transmitted through to the right side. This may cause an increased acceleration of the blood expelled from the right ventricle in the early part of the systole. Such an increased acceleration acting against the inertia of the column of blood in the pulmonary arterial tree may account for the discrepancy between the right ventricular and pulmonary arterial pressures at this point of the cycle. It would also account for the fact that the change in the shape of the pulse wave during ejection may occur along the pulmonary artery and not necessarily at the pulmonary valve. Even with an intact septum the pulmonary artery pressure can often be seen to lag a little behind the right ventricular pressure for a brief moment following the opening of the pulmonary valves. This is more obvious in the cases with pulmonary hypertension. The discrepancy between the curves, however, has been nowhere so great as in these two cases. Dillon and Schreiber (1948) found an increase in right ventricular systolic pressure on opening an interventricular shunt in animals but there was no alteration in the pressure curve. Joly *et al.* (1951) found the right ventricular systolic pressure to exceed the pulmonary artery systolic pressure by as much as 25 mm. Hg in two of their series of 21 patients with ventricular septal defect but do not mention whether this was associated with any particular contour of the pulse in the right ventricle. Similarly, one of the three patients with ventricular septal defect studied by Handelsman *et al.* (1948) had pressures of 72/3 and 49/20 mm. Hg in right ventricle and pulmonary artery respectively. It must be added, however, that Greene *et al.* (1949) found such a discrepancy in idiopathic dilatation of the pulmonary artery where there was no evidence of a ventricular septal defect.

In both of the patients with Eisenmenger's complex the right ventricular pulse wave was of the type seen in pulmonary hypertension. The ejection phase was found to correspond with the aortic tracing in one patient and with the pulmonary artery tracing in the other. Unfortunately in neither instance were both great vessels entered. In many previously published cases the systolic

pressures in pulmonary artery and right ventricle have been shown to be identical (Bing *et al.*, 1947; Dexter *et al.*, 1950; Soulié *et al.*, 1950; Cosby *et al.*, 1951; Goldberg *et al.*, 1951), while the systolic pressures in right ventricle and aorta were found to be identical by Cosby *et al.* (1951) and Voci *et al.* (1952). The case reported by the last authors is unique in the completeness of its physiological data and the systolic pressures in aorta, pulmonary artery, and both ventricles were shown to be the same. It seems probable, therefore, that in Eisenmenger's complex the shape of the pressure tracing during the ejection phase is identical in both great vessels and both ventricles. The right ventricular systolic pressure curves shown in the cases of Goldberg *et al.* (1951) and Voci *et al.* (1952) and in Fig. 23 of the paper of Soulié *et al.* (1950) all show the features here described as characteristic of pulmonary hypertension, and the ejection phase appears to be shaped by the curve of pressure in the great vessels.

Too few patients with Fallot's tetrad have been studied to warrant inclusion in this report, since the right ventricular pulse wave in this condition seems to vary in shape from case to case. Indeed, with all the varying degrees of dextroposition of the aorta and size of ventricular septal defect, and with the different types and degrees of pulmonary stenosis, one would hardly expect the curve to have a constant and characteristic appearance.

Summary

A study has been made of the right ventricular systolic pulse wave recorded during cardiac catheterization.

Where the pulmonary valve is normal, the shape of the wave is modified during the ejection phase and corresponds with the curve of pressure in the pulmonary artery. Differences in this shape are noted between patients with normal and patients with high pressure in the pulmonary artery. The presence of pulmonary valvular stenosis converts the pulse wave into a smooth rounded hump. With pulmonary infundibular stenosis this is not so.

Similar studies on three patients with ventricular septal defects, and two with Eisenmenger's complex are described.

My thanks are due to the physicians of King's College Hospital who have kindly allowed me to study their patients. In particular I am grateful to Dr. Terence East and Dr. Samuel Oram for their advice and encouragement. I am also indebted to Dr. J. L. V. Summerhayes and Miss G. M. Maxted for their help.

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SECONDARY TUMOURS OF THE HEART AND PERICARDIUM

BY

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It is perhaps not sufficiently widely realized that secondary tumours of the heart and pericardium are fairly commonly found at necropsy although they are rarely causes of clinical heart disease. It was thought worth while, therefore, to review the clinical records of cases of metastatic tumours of the heart and pericardium found at necropsy to see what evidence of their presence such tumours had produced during life.

Incidence and Distribution

Out of 4687 consecutive post-mortem examinations performed in the Western Infirmary, Glasgow during the years 1940–1953, there were 1270 cases of malignant disease of which 126 (10 per cent) showed secondary tumours of the heart or pericardium. Since a special search for cardiac involvement was not made in these routine necropsies, it is clear that the true incidence is likely to be higher than this, and that in some instances where only single metastases have been reported, multiple involvement may have been present. The primary sites of tumours invading the heart and pericardium are shown in Table I, and Table II shows the distribution of the secondary tumours where these were found in the heart itself. Willis (1952) gives a full description of the appearance of such tumours, and their mode of spread.

Clinical Features

Tumours of the heart and pericardium are often clinically silent, and even when they produce symptoms or signs, these are usually overshadowed by the effects of the primary tumour or a metastasis to another organ. In only 20 of the 127 cases in the present series was the attention of the clinician drawn to the heart, although examination of the cardiovascular system often revealed isolated or minor abnormalities (such as poor quality of heart sounds or occasional extrasystoles) which did not arouse clinical interest. Terminal circulatory failure was common. The correct diagnosis of the cardiac pathology was never made during life in the cases reviewed.

The following summarizes the types of clinical picture that directed the physician's attention specifically to the heart in 20 cases. Congestive cardiac failure was the presenting feature in 9, in 6 of which the existence of malignant disease was also recognized. In 7 cases there was chest pain thought to originate in the heart or pericardium, and in 4 of these myocardial infarction was suspected clinically, although in only two did the electrocardiogram support this diagnosis. Pericardial friction was noted in 6 cases. Two cases are included in the group because they presented poor quality heart sounds and electrocardiographic evidence of myocardial damage.

Arrhythmias commonly occurred in the group, sometimes being the only feature of the case to direct attention to the heart. Six patients had paroxysms of auricular fibrillation (cardiographic diagnosis was established in only one of these), and two had paroxysms of supraventricular tachycardia.

Electrocardiograms were taken in 15 of the cases and all were abnormal, showing myocardial changes, myocardial damage, the presence of an arrhythmia, or changes suggestive of coronary

TABLE I

PRIMARY SITE OF TUMOURS WITH METASTASIS IN HEART OR PERICARDIUM, OR BOTH

	Number of cases necropsied	Metastases to heart only	Metastases to heart and parietal pericardium	Metastases to parietal pericardium only
Malignant melanoma	7	2	2	0
Carcinoma				
Bronchus	272	23	19	43
Liver	14	1	0	0
Kidney	29	1	0	1
Breast	38	0	0	2
Œsophagus	38	0	0	1
Pancreas	41	1	0	0
Colon	146	2	0	0
Stomach	185	1	0	1
Penis	1	0	1	0
Thymus	1	0	0	1
Trachea	2	0	0	1
Mesodermal tumours				
Lymphadenoma	23	3	1	1
Sarcoma	15	3	0	0
Reticulosarcoma	28*	2*	1	2
Lymphosarcoma	12	0	0	2
Lymphoid tumour	6	1	0	0
Multiple myeloma	18	2	0	0
Monocytic leukæmia ..	9*	1*	0	0
Lymphatic leukæmia ..	23	2	0	0
Myeloid leukæmia	23	2	0	0
Leiomyosarcoma	3	1	0	0
All other tumours	337	0	0	0
Total	1270	47	24	55

* One case with reticulosarcoma and monocytic leukæmia co-existing had tumour in the heart. It is included in the Table under both headings but appears only once in the total.

TABLE II

PATHOLOGICAL FINDINGS IN 71 CASES OF METASTASIS INVOLVING THE HEART

Feature considered	Number of cases in which detail is available		Incidence
Single or multiple metastases	57	Single Multiple	25 32
Side of heart affected	43	Left side only Both sides Right side only	16 15 12
Part of heart affected	49	Atria Ventricles Atrial septum Ventricular septum Cavity of heart Coronary artery	24 32 2 5 2 1
Layer of heart affected	63	Epicardium Myocardium Endocardium	39 29 8

artery thrombosis. It is of interest that tracings from two patients who had tumours of the left atrium had abnormal P waves, one in leads I and II, and the other in leads II and III.

The following example shows the difficulty that may arise in the diagnosis of metastatic tumour of the heart or pericardium.

Case Report. A boilerman, aged 48, was admitted to hospital on 11/10/49, with a history of severe breathlessness of sudden onset four days previously. The breathlessness was accompanied by a tight feeling at the lower end of the sternum and at the back of the neck, profuse sweating and weakness. He went home to bed at once and the feeling of tightness passed off after 24 hours. All his symptoms improved till the day of admission when severe breathlessness and sweating recurred. Since the illness began he had lost his appetite and been troubled with gastric flatulence.

There was no relevant previous illness or familial disease, but the patient stated he had had " neuritic " pains in the left shoulder for eight months and had lost some weight during that period. For a month he had had a constant vague feeling of upper abdominal discomfort unrelated to food but associated with rumbling in his abdomen.

Examination showed the patient's temperature to be 97·0° F., pulse 100 a minute, and respirations 28 a minute. He was restless, cyanosed, a little pale, and sweating. There was distension of the neck veins but no œdema. Slight clubbing of the fingers was present.

The pulse was irregular in rhythm and force. The radial and brachial arteries were sclerosed. The blood pressure was 120/80. The apex beat was palpable in the fifth intercostal space 10 cm. to the left of the mid-sternal line. The heart sounds were quiet and of poor quality. No murmurs or pericardial friction were heard.

The percussion note was slightly impaired and medium and fine moist sounds were heard at both lung bases, especially the right. The liver was not palpable but percussion showed it to extend 3·7 cm. below the costal margin. No abnormality was present in the nervous system.

Examination of the blood showed Hb 12·6 g. per 100 ml. and white cell count 10,800 per c.mm. The urine was normal.

X-ray of chest (Fig. 1) showed that the heart shadow was considerably enlarged and there was general congestion in the lungs with infiltration at the bases. On screening there was paradoxical movement of the left dome of the diaphragm. The radiologist thought there was probably a neoplasm involving the lower bronchus on the left side, together with signs of cardiac failure.

Electrocardiogram (Fig. 2) showed auricular extrasystoles and electrical alternation in leads I, CR4, and CR2. There was slurring of QRS in leads I, II, and III and inversion of T waves in leads II and III. These findings, taken with the clinical history, were interpreted as the result of a posterior coronary artery thrombosis.

The blood pressure rose to 145/85 during the next two days without change in the physical signs or electrocardiogram. On 16/10/49 pericardial friction was heard, and from that date he had paroxysms of dyspnœa which gradually became more frequent: the pulse became faster, more irregular, and weaker, and after a short period of Cheyne-Stokes respirations the patient died on 18/10/49.

The diagnosis at necropsy was bronchial carcinoma extending to parietal pericardium, hæmorrhagic pericardial effusion, and acute cardiac failure. A carcinoma was found arising in a small bronchus posterior to the hilum in the lower lobe of the left lung. The tumour had spread directly for 2 cm. to involve the left side of the parietal pericardium with a plaque 5 cm. in diameter. The pericardial sac contained 700 ml. of heavily blood-stained fluid, and the surfaces were dulled by deposition of an irregular film of fibrin. Apart from fibrin on the epicardium the heart was normal, and the coronary arteries were healthy. Both pleural cavities were largely obliterated by fibrous adhesions. Congestion was present in lungs, liver, kidneys, and spleen.

Comment. In this case the physician was confident that the patient had died as a result of myocardial infarction in spite of a rather atypical history and evidence that there was a co-existent bronchial carcinoma.

All the cardiac manifestations of the case can be ascribed to acute cardiac tamponade five days before admission to hospital. That Claude Beck's triad of acute cardiac compression (small quiet heart, raised venous pressure, and arterial hypotension) was incomplete is explained by the patient's survival for five days giving the pericardium time to stretch and allowing the blood pressure to rise.

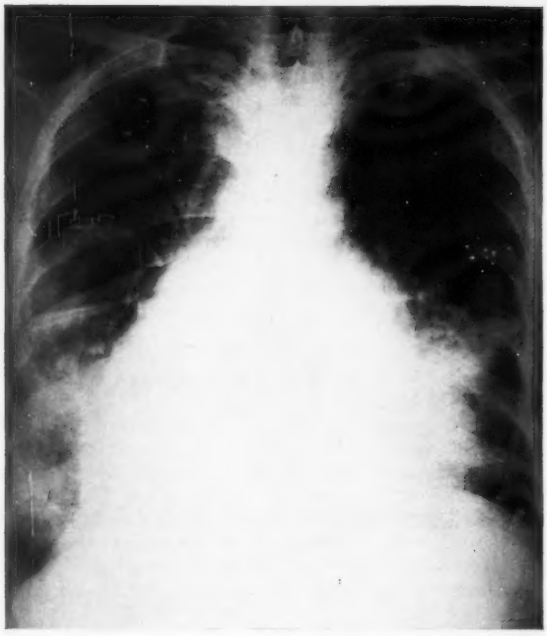

FIG. 1.—Radiogram four days after the onset of acute hæmopericardium due to bronchial carcinoma arising in the left lower lobe of lung.

Inversion of T waves in leads II, III, and CR7, strongly suggests posterior coronary artery thrombosis, but is also compatible with pericarditis on the fifth day of the illness (Nay and Boyer, 1946). Had the patient been seen earlier in the illness, S–T changes indicative of pericarditis and not of coronary thrombosis would probably have been present. Slurring of the QRS segment favours coronary artery disease (Barnes and Burchell, 1942). Electrical alternation as a result of malignant disease causing hæmopericardium has been described by Feldman (1938) and Reisinger *et al.* (1942), and has been seen by Harvey and Whitehill (1937) in tuberculous pericarditis. It is tempting to explain the cardiographic changes and the retrosternal tightness on the basis of myocardial ischæmia resulting from external compression.

DISCUSSION

The post-mortem incidence of secondary tumours of the heart and pericardium in this series (10%) compares with that found by Scott and Garvin (1939) who, in a series of 1082 cases of malignant disease, found the heart or parietal pericardium involved in 118 cases (10·9%). De Loach and Haynes (1953) in 980 patients suffering from malignant disease found 137 instances (13·6%) of involvement of the heart and pericardium. The importance of bronchial carcinoma, which frequently metastasizes to the heart or pericardium (31% in this series of 272 cases), has often been demonstrated and is explained by the great invasiveness of that tumour, and the proximity of the primary growth and its mediastinal secondaries to the pericardium. Contrary to the usual findings, in this series carcinoma of the breast is a relatively rare tumour to metastasize to the heart and pericardium. Both sides of the heart are involved with roughly equal frequency, a finding similar to that of Scott and Garvin (1939) and Willis (1952), but at variance

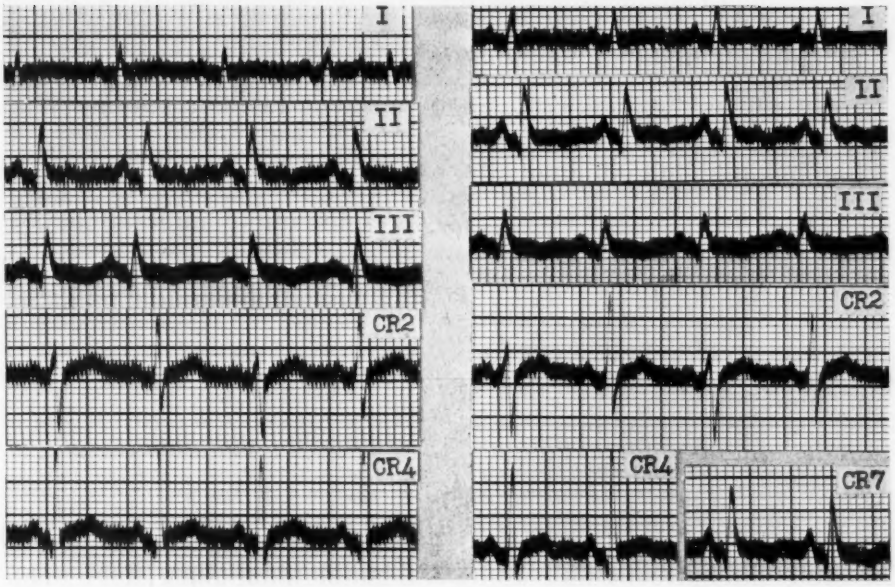

FIG. 2.—(A) Electrocardiogram taken 4 days after onset of acute hæmopericardium. Auricular extrasystoles (I and III), electrical alternation (I and CR2), and inverted T waves (II and III) are seen. CR7 was not recorded. (B) Electrocardiogram taken the day before death. There are now no auricular extrasystoles, and CR7 shows inverted T waves. Otherwise the tracings are unchanged.

with Prichard (1951) and De Loach and Haynes (1953) who found the right side more frequently involved than the left.

Detailed clinico-pathological correlation is difficult since clinical attention is so seldom directed to the heart, and the clinical picture produced is so diverse. Mahaim (1945) described some interesting cases. Often it is difficult to imagine why a metastatic tumour has not caused clinical manifestations of heart disease. The explanation may lie in the tendency of tumour tissue to compress and displace heart tissue rather than to bring about its destruction and result in gross interference with the functions of contraction and conduction. From the present study it is felt that clinical manifestations of heart disease are more often due to pericardial reaction to tumour tissue than to the direct effect of the tumour on the heart's action. Of the 20 cases in which clinical attention was drawn to the heart, 8 came from a group of 17 cases who had 100 ml. or more of blood-stained pericardial effusion, and 3 came from a group of 7 who had fibrinous or serofibrinous pericarditis, leaving only 9 cases from the group of 102 who did not have a pericardial reaction.

Prichard (1951) states that about 20 ante-mortem diagnoses of metastatic cardiac tumours have been published, the diagnosis usually being based on the development of a cardiac arrhythmia in a patient known to have widespread malignant disease. Certainly the diagnosis should always be suspected in such patients with cardiac symptoms or signs, but it can only be confirmed during life by finding malignant cells in pericardial fluid, by radiological study of the cardiac outline after induction of pneumopericardium, or at operation. As a diagnostic procedure tapping of a pericardial effusion is the only method that seems justifiable since the diagnosis can seldom be of value to the patient. Blotner and Sosman (1944) have described a case of leukæmia in which symptoms due to heart block were relieved by restoration of normal cardiac rhythm with radiotherapy. It is worth noting that heart block is a very rare manifestation of metastatic tumours of

the heart. Electrocardiography is of little value in the diagnosis or localization of metastatic tumours of the heart or pericardium.

Summary

Metastatic tumours of the heart and pericardium are found in about 10 per cent of all patients dying of malignant disease. Bronchial carcinoma is the most important primary site. Clinical manifestations of these tumours are rare, and are more often due to pericarditis than to the direct effect of the tumour itself.

An illustrative case is described in some detail.

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THE ELECTROCARDIOGRAM IN PRIMARY ENDOCARDIAL FIBROELASTOSIS

BY

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Primary endocardial fibroelastosis (EFE) in infancy has become a widely recognized pathological entity but it is only latterly that clinical diagnosis has been attempted. Although there are now numerous reports of the clinical picture of the disease, electrocardiographic studies are scanty.

Before 1953 there were 30 electrocardiograms of previously reported cases (Weinberg and Himelfarb, 1943; Vulliamy, 1947; Craig, 1949; Glynn and Reinhold, 1950; Stadler *et al.*, 1950; Lewis, 1951; Emery and Illingworth, 1951; Collier and Roshan, 1951; Hill and Reilly, 1951; Edmonds and Seelye, 1951; Blumberg and Lyon, 1952; Johnson, 1952; Bonham-Carter *et al.*, 1952; Prec and Cassels, 1952). Rhyhtm disturbances were noted in fourteen: auricular tachycardia in two; nodal rhythm with short P–R interval in one; and paroxysmal multifocal ventricular extrasystoles in one instance. Alterations in conduction occurred in about one-third of the cases: prolonged P–R interval in six and atrio-ventricular dissociation in five cases; the latter finding was observed at, or shortly after, birth in four tracings. Bundle branch block was rare—left once and right three times. A slight or moderate degree of right axis deviation was present in 14 instances, left axis deviation occurring only once. Flattening or inversion of the T wave in two or all of the standard leads was reported in 10 patients.

Since 1952 several complete electrocardiograms have been published (Adams and Katz, 1952, 1953; Clément *et al.*, 1952; Schweisguth and Nouaille, 1952; Lambert *et al.*, 1953; Leteer, 1953; Metianu *et al.*, 1954). It has become increasingly clear in this period that the electrocardiogram will assist clinical diagnosis. Most authors note left ventricular hypertrophy to be present.

The purpose of this paper is to analyse the electrocardiographic findings in a relatively large group of cases with post-mortem confirmation.

MATERIAL

Twenty-three electrocardiograms with standard, unipolar limb and præcordial leads have been assembled. Ten of these have been published (Adams and Katz, 1952, 1953; Clément *et al.*, 1952; Schweisguth and Nouaille, 1952; Leteer, 1953; Lambert *et al.*, 1953; Metianu *et al.*, 1954). Of the remaining cases, seven were patients in the Children's Memorial Hospital, Montreal and the Children's Hospital, Buffalo, New York, while six were observed in the Hospital for Sick Children, Toronto. The age at death in this group ranged from two months to seven years. All had an anatomical diagnosis of primary endocardial fibroelastosis with or without valvular involvement. None of these patients was found to have evidence of coronary calcification or myocardial infarction at necropy. Only one had an associated congenital anomaly of the heart (Case 21 with preductal

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coarctation of the aorta). In five instances (Cases 4, 5, 15, 16, and 17) there was mention in the necropsy protocols of cellular infiltration of the myocardium in addition to the characteristic mural endocardial thickening and marked left ventricular hypertrophy. In 20 instances where complete clinical and pathological data were available, heart failure with pulmonary congestion, hepatomegaly, and dilated right atrium and ventricle was a prominent feature terminally.

Electrocardiographic Criteria of Ventricular Hypertrophy

Left Ventricular Hypertrophy. The presence of two or more of the following signs has been taken as direct evidence of left ventricular hypertrophy.

1. Voltage of R in V5 or V6 greater than the maximum normal for age.*
2. Voltage of S in V1 or V2 greater than the maximum normal for age.
3. Secondary T wave inversion in V5 and/or V6.
4. Ventricular activation time in V6 greater than maximum normal for age.
5. R/S ratio in V1 (Gros *et al.*, 1951): less than 1·0 under the age of 1 year; less than 0·3 between 1 and 5 years; and less than 0·1 after 5 years.

In addition, *in the presence of direct signs of right ventricular hypertrophy*, indirect evidence of left ventricular hypertrophy is believed to be provided by the persistence of a Q wave in V5 and/or V6 in the presence of clockwise rotation and the absence of right bundle branch block.

Right Ventricular Hypertrophy. Taken as *direct* signs of right ventricular hypertrophy were at least one of the following.

1. Voltage of R in V1 or V2 greater than the maximum normal for age.
2. Voltage of S in V5 or V6 greater than the maximum normal for age.
3. Ventricular activation time in V1 greater than the maximum normal for age.

Electrocardiographic Findings

Rhythm. Apart from Case 8 which showed persistent multifocal extrasytoles, sinus rhythm was the rule.

Conduction. The shortest P–R interval was in a case with Wolff-Parkinson-White (W-P-W) syndrome (Case 22). The P–R interval was prolonged in less than one-third of the cases and may be so before the administration of digitalis (Case 6). Complete heart block was not encountered in this series. Partial right bundle branch block or complete left bundle branch block appears to be uncommon (once each).

P Wave. In 14 cases the P wave showed abnormalities: right auricular hypertrophy alone was present in two; left auricular hypertrophy alone in nine, and combined auricular hypertrophy in three cases.

QRS Complex. Apart from the cases of W-P-W syndrome and left bundle branch block the duration of QRS was normal. Sixteen cases had vertical or semi-vertical electrical position, $\hat{A}$QRS usually between $+80^{\circ}$ and $+100^{\circ}$, prominent S1, and clockwise rotation. Three cases occupied an intermediate position, having the $\hat{A}$QRS at $+30^{\circ}$, while two showed also anticlockwise rotation with Q in lead I. Semi-horizontal position occurred four times under special circumstances, viz: left bundle branch block (Case 23), complicating congenital anomaly (Case 21) and marked right ventricular hypertrophy (Cases 1 and 17). Left axis deviation ($\hat{A}$QRS less than $+30^{\circ}$) was present only twice, in each instance the position being horizontal. Unipolar limb leads aVR had a predominantly negative deflection apart from Cases 1, 5, and 22. The voltage in aVL and aVF was normal with the exception of Case 21. The QRS pattern over the right præcordium was commonly rS and over the left præcordium qR. The transitional complex tended to be shifted to the left. With the exception of Case 22, the ventricular activation time was always longer in V6 than in V1 with the exception of Case 1. It exceeded the normal value for age in V6 in nine and in V1 in three cases.

* Maximum normal values for age are based on those of Ziegler (1951).

T Wave. Inversion of T waves in the left-sided chest leads was extremely common, only three cases not showing this abnormality. The T wave may be inverted in any standard lead but it was abnormal in I and/or II in two-thirds of our cases.

S–T Segment. This was normal or only slightly depressed in all cases except that with the W-P-W syndrome.

Discussion

Three of 23 cases in this series have electrocardiograms that are completely different from the remainder (Table I). One (Case 21) has no evidence of ventricular hypertrophy and left auricular

TABLE I

Pattern	No. of Cases
No ventricular hypertrophy—left auricular hypertrophy only	1
Complete left bundle branch block	1
W-P-W syndrome	1
Left ventricular hypertrophy	16
Right ventricular hypertrophy	4
Total	23

Auricular hypertrophy: left 9, right 2, combined 3

hypertrophy was its sole anomaly; a second (Case 22), exhibited W-P-W syndrome, and a third (Case 23) showed complete left bundle branch block. While the first and last tracings associated with cardiomegaly may only suggest left ventricular disease, this may still be an important diagnostic clue on occasion.

Left Ventricular Hypertrophy. Electrical changes due to left ventricular enlargement or thickening are recorded in 16 of the 23 cases. The criterion invariably satisfied in these was T wave inversion in V6. Abnormally tall R in V6 (75%) or low R/S ratio in V1 (64%) were common. Delayed ventricular activation time in left chest leads (53%) or increased voltage of S in V1 (40%) were less frequently encountered.

Reduced electrical potentials may occasionally be encountered (Fig. 1). Such factors as myocardial anoxæmia, pleuro-pericardial effusion or œdema due to cardiac failure in its terminal stages may be responsible for this phenomenon as in Case 2 and Case 9. With the exception of the few cases with anatomical complications (coarctation of the aorta, Case 20) or conduction disturbances (Cases 21 and 22) the electrocardiogram followed more or less the same pattern: vertical or semivertical position, tall R or qR waves in V5 and V6 with secondary inversion of the T wave (Fig. 2).

Right Ventricular Hypertrophy. Because there is difference of opinion as to whether a heart in vertical electrical position with clockwise rotation and left ventricular hypertrophy indicates combined ventricular hypertrophy, we have avoided attaching significance to its presence. None the less, over half of the remaining 13 cases showed this combination.

In four instances (Cases 1, 5, 15, and 17) the initial electrocardiograms showed predominant signs of right ventricular hypertrophy. These are the only examples of frank right axis deviation ($\hat{A}QRS$ over $+100°$). Predominance of the positive deflection over the right præcordium is frequent (three of four cases). Even qR patterns due to extreme right heart overload may be recorded as in Case 1 (Fig. 3). Two of these cases also showed a horizontal electrical position, a sign only rarely encountered in the majority group and then confined to the complicated cases (coarctation of the aorta; left bundle branch block).

Only one of this particular group (Case 17) failed to show some left ventricular hypertrophy on subsequent tracings. In fact even in the initial electrocardiograms there were findings suggestive of this eventuality in three instances: diphasic or negative T waves in V5 or V6 twice, Q waves and long ventricular activation times over the left of the præcordium in the presence of marked clockwise rotation.

Two cases observed in this centre at the height of the initial congestive heart failure and subsequently over a period of many months showed startling reversal of electrocardiographic pattern. In one (Fig. 6) right ventricular hypertrophy was replaced (with the relief of symptoms) by pure left ventricular hypertrophy

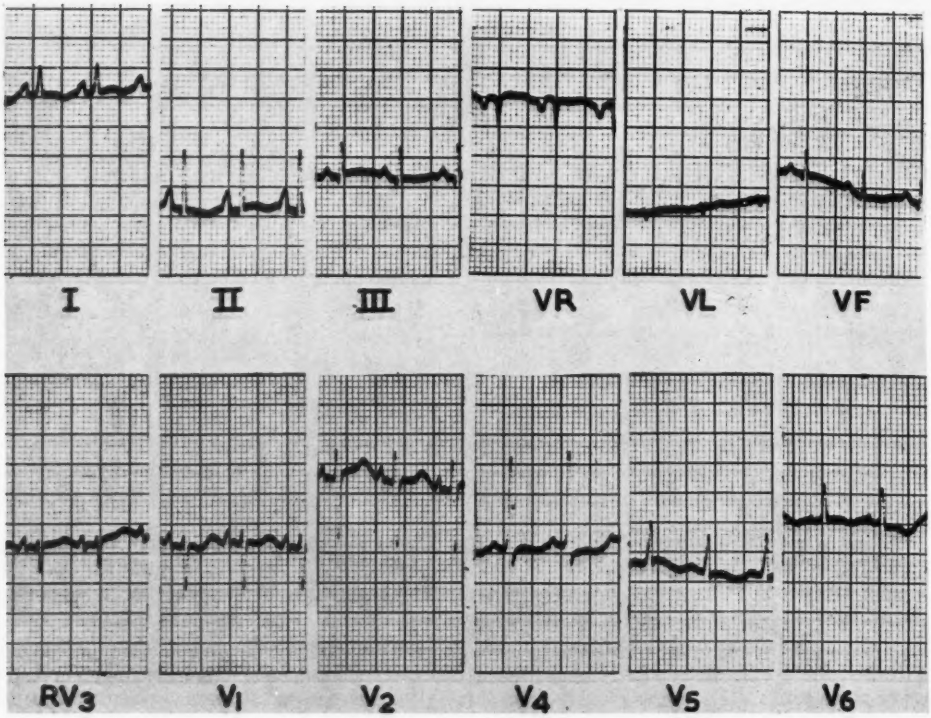

FIG. 1.—Boy, aged 2 months (Case 2), 8/12/52. Despite the lack of increase in voltage of QRS this tracing shows left ventricular hypertrophy on the basis of predominant negative deflections over the right and predominant R with negative T waves over the left præcordium. The autopsy showed marked left ventricular hypertrophy and pleuro-pericardial effusion.

electrically. This phenomenon was repeated in three later bouts of heart failure. Case 1, also improved by digitalis, was seen to have left ventricular hypertrophy in the electrocardiogram after four months of treatment. Three further cases (Cases 6, 9, and 21), while presenting predominant left ventricular hypertrophy, and included for that reason in the majority group, had associated direct signs of right ventricular hypertrophy such as abnormally high voltage of R in V1 or V2 (Fig. 4).

The practical application of this information is, of course, that EFE need not necessarily be excluded from the differential diagnosis merely because of the lack of left ventricular strain in the cardiogram. On the other hand it is striking that all the patients with marked right ventricular hypertrophy either had a chronic course, as in Case 1, or were atypical anatomically, as in Case 17 (of Metianu) with four chamber involvement and mild endocardial changes. Fulminating cases by comparison have not shown any right ventricular hypertrophy in this series.

Edwards (1953) has suggested recently an anatomical division of primary endocardial fibroelastosis into a 'contracted' type with a small left ventricle and a dilated and greatly hypertrophied right heart, and a 'dilated' type with a dilated and noticeably hypertrophied left ventricle. From an electrocardiographic viewpoint it is possible that the group with predominant or associated direct signs of right ventricular hypertrophy are the cases of the "contracted" type, whereas the others may well correspond to the 'dilated' type.

Auricular Enlargement or Hypertrophy. Signs of auricular enlargement in the electrocardiogram were almost always noted in cases showing direct signs of right ventricular hypertrophy (Fig. 4). It was rather

less frequently seen in the cases with left ventricular hypertrophy. Chronicity of symptoms seemed to be the important factor governing this change.

It is not suggested that the electrical pattern so commonly encountered in primary endocardial fibroelastosis is specific for this condition. Identical changes may be recorded in patients suffering from coarctation of the aorta, patent ductus arteriosus, complete transposition of the great vessels, truncus arteriosus, tricuspid atresia with transposition of the great vessels, and aortic stenosis. There are means other than electrical by which endocardial fibroelastosis may be differentiated from such anomalies. However, extreme left ventricular hypertrophy in an infant with preductal coarctation of the aorta in congestive heart failure would suggest its association with EFE. Infants with physical signs of ventricular septal defect but marked left heart strain in the cardiogram may be similarly suspect.

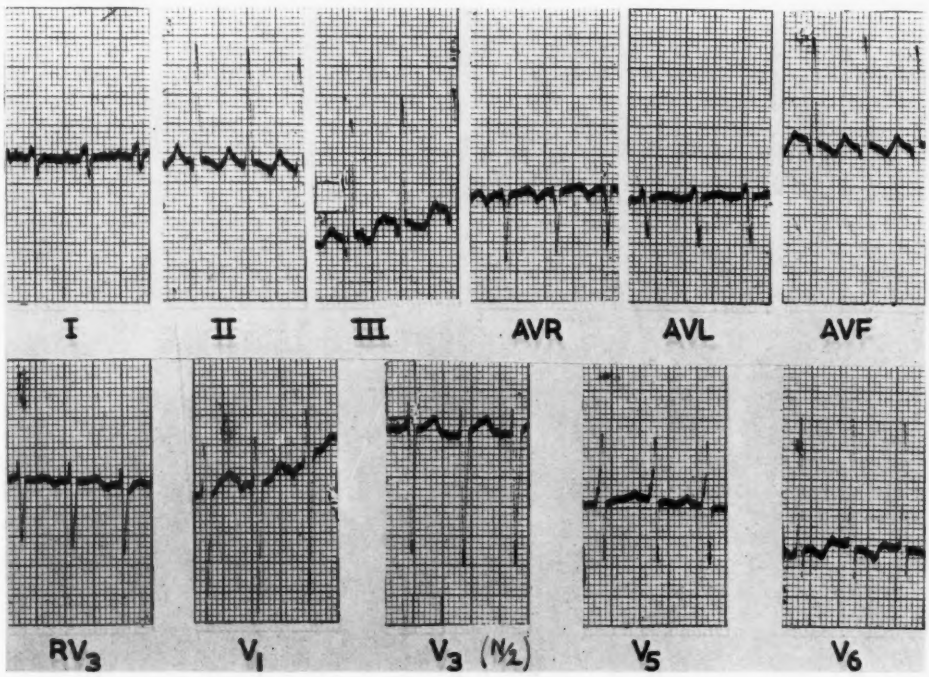

FIG. 2.—Girl, aged 17 months (Case 18), 11/3/53. The common pattern in this series: vertical electrical position; marked clockwise rotation; high voltage of QRS; inverted T wave over the left præcordium (left ventricular hypertrophy).

The conditions in which the electrocardiogram renders crucial aid in ætiological diagnosis are found in the group of large hearts with failure in infancy unaccompanied by central cyanosis, murmurs, or shunts. This clinical picture is presented by endocardial fibroelastosis, interstitial myocarditis, glycogen disease of the heart, and left coronary artery arising from the pulmonary artery (LCPA).

According to Miller (1954) the electrocardiogram in glycogen disease of the heart shows a left heart strain pattern characterized by severely depressed S–T segments with sharply inverted T waves in the limb leads. The same author believes that in interstitial myocarditis general flattening or loss of amplitude of T waves in every lead in which the QRS complex is upright and minimal S–T segment changes with variations from record to record form a dependable electrical pattern. Others feel that the development of conduction disturbances is a helpful sign.

There has been more noticeable difficulty in distinguishing endocardial fibroelastosis from the much less frequent syndrome of left coronary artery arising from the pulmonary artery. While no case of endocardial

fibroelastosis has shown signs of myocardial ischæmia, injury or necrosis,* seven of the eight complete tracings in LCPA (McKinley *et al.*, 1951; Dagonet, 1952; Holzmann, 1952; Taussig, 1953; Keith, 1954; Miller, 1954; Schlichter *et al.*, 1954) have signs of myocardial infarction of the anterolateral, anteroseptal or high anterolateral types (Fig. 5). A Q wave in lead I was rare in EFE (3 of 23 cases), was always part of a qRs pattern, and was positional. In LCPA it was frequent (15 of 19 cases: Bland, *et al.*, 1933; Eidlow and Mackenzie, 1946; Lyon, *et al.*, 1946; Kaunitz, 1947; Gasul and Loeffler, 1949; Gouley, 1950; McKinley, *et al.*, 1951; Dagonet, 1952; Hartenstein and Freeman, 1952; Holzmann, 1952; Keitzer and Rochat, 1952; Taussig, 1953; Keith, 1954; Miller, 1954; Schlichter, *et al.*, 1954), and was part of a qR or QR complex, being usually the result of necrotic changes. The presence of such ischæmic and necrotic findings should exclude EFE but does not, of course, rule out other causes of myocardial infarction in infancy, such as coronary

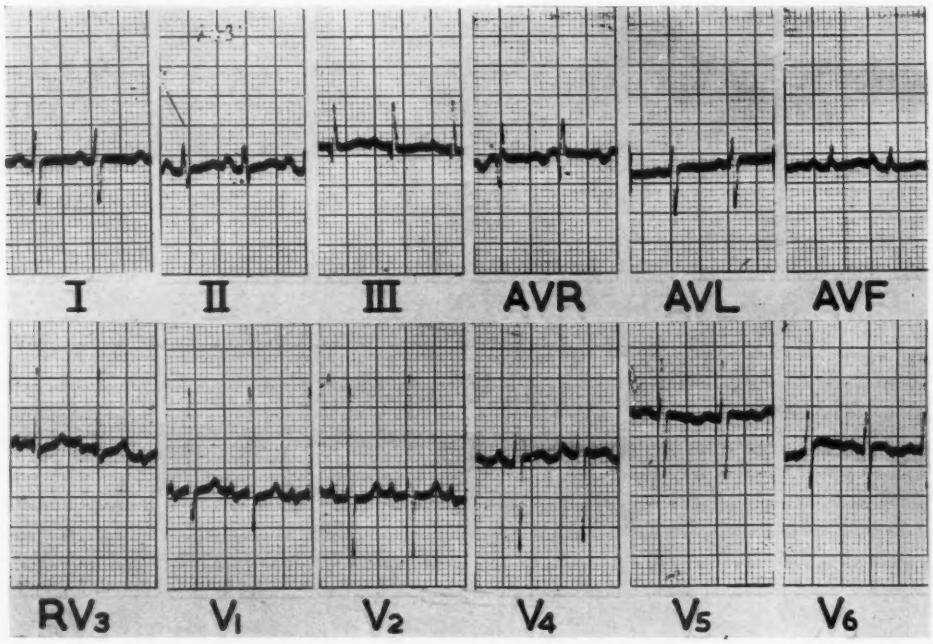

FIG. 3.—Boy, aged 3 weeks (Case 1), 5/1/53. Electrocardiogram showing frank right ventricular hypertrophy including a qR pattern in the right præcordial leads.

calcification, myocardial tumours, periarteritis nodosa, or coronary atherosclerosis. Ischæmic changes may be obtained also from the dying heart. Complete left bundle branch block with widening of the QRS has been encountered in both conditions, but possibly its appearance at an early age may favour LCPA. Low voltage T wave inversion in the standard leads may be seen in both conditions. The flattening may be due to generalized myocardial hypoxæmia, diffuse generalized fibrosis of the myocardium, or extracardiac collections of fluid. Where T wave change is due to hypertrophy as in EFE, the shape is asymmetrical; where it is the result of infarction, the T wave is symmetrical with late inversion and is seen in other leads of the electrocardiogram.

Coronary calcification, another condition that may have the same clinical picture as LCPA or EFE, is interesting because it may show the electrocardiographic features of both: vertical or semivertical heart with clockwise rotation and left ventricular hypertrophy, and, in addition, signs of ischæmia or necrosis of the apex and the antero-lateral wall of the left ventricle.

* Case 22 (Leteer, 1953) was reported as showing subendocardial ischæmia, but because of the presence of W-P-W syndrome it is difficult to ascribe significance to S–T segment changes.

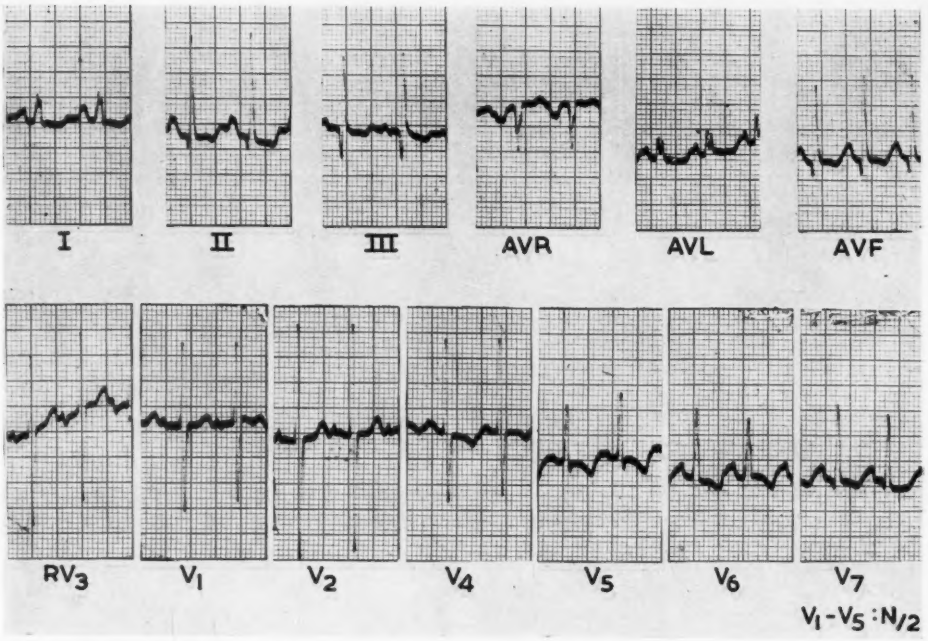

FIG. 4.—Girl, aged 3½ months (Case 6), 18/12/52. This tracing shows in addition to the obvious signs of left ventricular hypertrophy (high voltage R wave and T inversion in the left chest leads) tall R waves over the right præcordial leads indicating right ventricular hypertrophy or dilatation.

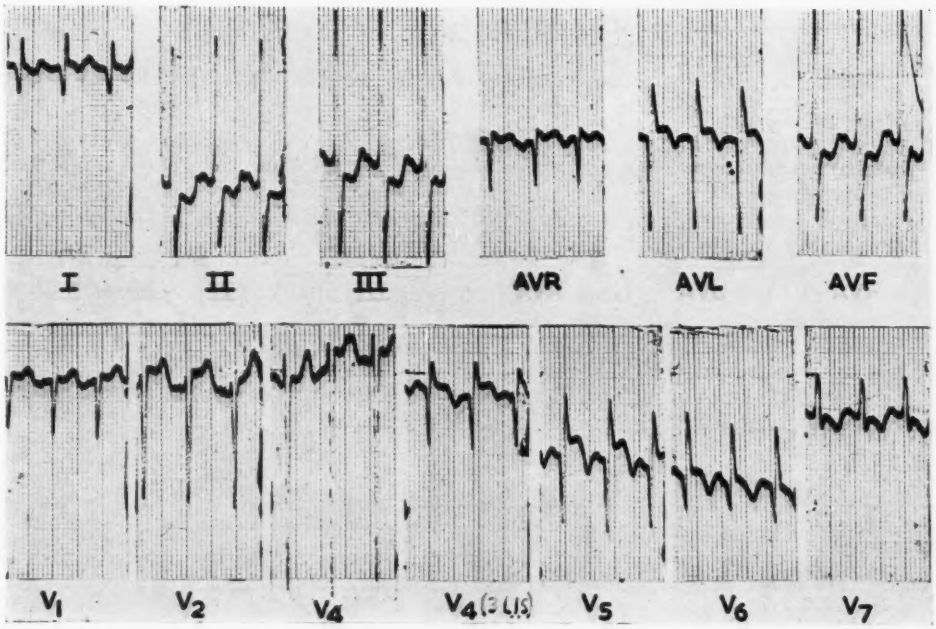

FIG. 5.—Boy, aged 4 months. Electrocardiogram of a case of left coronary artery arising from the pulmonary artery showing antero-lateral infarct.

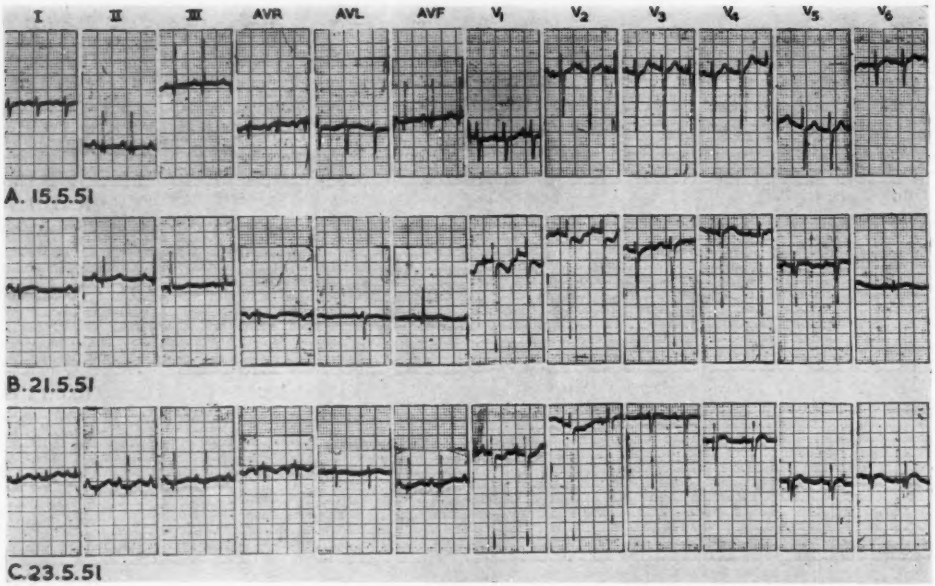

FIG. 6.—Girl, aged 13 months. Electrocardiograms illustrating the findings in Case 15. (A) In congestive heart failure before digitalization: vertical electrical position with an ÂQRS of +120°, transitional complex and q wave in V6. Note that the only suggestion of left ventricular hypertrophy lies in the persistence of q wave in V6 and the ventricular activation time in V6 being longer than in V1. (B) After two days on digoxin: ÂQRS now +90°, transitional complex in V5, q waves in V5 and V6, depth of S in V1 increased four times and S in V6 only 1 mm. (C) After four days on digoxin: ÂQRS +80°, transitional complex in V4, q waves in V4, V5, and V6 and a deep S in right chest leads.

In the first tracing the left ventricular hypertrophy is overshadowed by the marked right ventricular dilatation, but as the congestive failure clears the signs of left ventricular hypertrophy become very obvious.

SUMMARY

Twenty-three complete electrocardiograms of cases of primary endocardial fibroelastosis proven at necropsy are analysed.

There was a high incidence (16 cases) of left ventricular strain in hearts with vertical or semi-vertical electrical position.

Right ventricular hypertrophy occurred relatively commonly either in a pure form (4 cases) which might or might not be replaced later by left ventricular hypertrophy, or in the form of combined ventricular hypertrophy (3 cases).

There was a frequent alteration of the P wave (14 cases) indicating right and/or left atrial hypertrophy or dilatation.

The value of the electrocardiogram as an aid to the differential diagnosis of endocardial fibroelastosis from a number of clinically similar conditions in infancy has been emphasized.

The authors wish to express their special appreciation to Dr. E. C. Lambert of the Children's Hospital, Buffalo, New York, Dr. A. L. Johnson of the Children's Memorial Hospital, Montreal, and Dr. Helen Taussig of Johns Hopkins Hospital, Baltimore for supplying electrocardiograms; without their generous co-operation this study would not have been possible.

Owing to space limitations, a table containing the electrocardiographic details of the individual cases has been omitted. It will be available with the authors' reprints.

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AORTIC VALVULAR STENOSIS WITH COARCTATION OF THE AORTA

WITH SPECIAL REFERENCE TO THE DEVELOPMENT OF AORTIC STENOSIS UPON CONGENITAL BICUSPID VALVES

BY

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The combination of coarctation of the aorta and aortic valvular stenosis is not well known, although the association of coarctation with aortic incompetence is generally recognized and usually attributed to an incompetent bicuspid aortic valve. Abbot (1928), in her review of coarctation, did not discuss its association with aortic valvular stenosis. However, she reported four cases of sub-aortic stenosis occurring with coarctation (an incidence of 2%), and Taussig (1947) regards this combination as occurring so frequently as to constitute a clinical entity. Wood (1950) states briefly that with coarctation " aortic or sub-aortic stenosis is by no means rare." Reifenstein *et al.* (1947) in their series of 104 post-mortem cases of coarctation record 11 with " calcific aortic stenosis " (each of which they regard as being due to rheumatic disease), but they do not enlarge upon this association. Recently Jacobson *et al.* (1953) have collected 14 reported cases of " calcific aortic stenosis " complicating coarctation, and add one further case; they comment on the surprising rarity of bicuspid aortic valves, which they found in only 3 of 14 necropsy cases [one (Gilbert *et al.*, 1950) lacks post-mortem confirmation], and on the rarity of calcific aortic valves.

Five cases of aortic stenosis complicating coarctation have recently come to our attention. This has prompted a review, from which we have collected 24 cases with necropsy confirmation of this combination.

Clinical Material

(*A*) *Present Series.* Five new cases of coarctation of the aorta with aortic valvular stenosis are reported; three of these have necropsy confirmation, the other two are living.

Case 1. Man, aged 43. A murmur was discovered on routine physical examination at school at 8 years. He was refused life insurance at 17 years, and high blood pressure was found at 22 years. For two years before admission he had complained of giddiness, sweating, and nervousness. On examination there was a systolic thrill and harsh systolic murmur in the second right intercostal space. The second aortic sound was normal. No diastolic aortic murmur was heard, but a mid-diastolic murmur was audible at the apex. A systolic murmur was heard over the back. The radial pulses were equal and the femoral pulses were weak and delayed. The blood pressure was 170/100 in both arms. A cardiogram showed left ventricular hypertrophy and auricular fibrillation. X-ray and screening revealed marked left ventricular enlargement, prominent ascending aorta, extensive rib-notching, but no left auricular enlargement. The patient died of a cerebral vascular accident with a left hemiplegia.

Necropsy. Severe coarctation immediately distal to the origin of the left subclavian artery, which admitted only a surgical needle. There was a marked collateral circulation. The pericardium was unusually

* During tenure of Beaverbrook Scholarship from McGill University.

thin. Both auricles were free from clot. The aortic valve was stenosed, with large calcified irregular cusps, and the left ventricle was hypertrophied. There was no mitral stenosis. There was a large embolus at the bifurcation of the right common carotid artery, apparently blocking both internal and external branches. Another embolus occluded the left internal carotid. There was infarction of the posterior part of the right internal capsule and of some of the right occipital lobe. The left kidney had numerous infarcts. A section of the ileum was gangrenous.

Microscopical sections of the aortic and mitral valves were not made. There was thickening of the pericardium over the auricle, and of the endocardial lining. The ventricle showed thickening of the endocardium and atheroma of the coronary arteries. Section of the heart muscle through the auriculo-ventricular junction showed perivascular fibrosis of the small vessels with persisting cellular elements.

Final diagnosis. Coarctation of the aorta, calcific aortic stenosis, multiple emboli, the source of which was not found, and possible rheumatic heart disease.

Case 2 (Dr. Goodwin's case). Woman, aged 18 years. She complained of dyspnœa on effort for six months. There was a systolic thrill and murmur, maximal in the second right intercostal space. The apex beat was heaving and of left ventricular type. The blood pressure was 190/120 in both arms. The femoral pulses were feeble and delayed. A cardiogram showed marked left ventricular hypertrophy. X-ray and screening showed left ventricular enlargement, a small aorta, and rib-notching. The patient died four hours after a resection of the coarctation from hæmorrhage at the suture line.

Necropsy. Bicuspid aortic valve, cusps thickened and orifice stenosed. Marked left ventricular hypertrophy. Microscopic sections from the various valves, valve rings, and left ventricle showed no signs of carditis.

Final diagnosis. Coarctation of the aorta and congenital bicuspid aortic valve with valvular stenosis.

Case 3 (Dr. Bret's case). Man, aged 18 years. A murmur was first discovered at eight years. At 12 years coarctation of the aorta was diagnosed. Dyspnœa had been noted from the age of ten. There had been two episodes of hæmoptysis within two years of death. On examination there was an aortic thrill and murmur, maximal in the second right intercostal space; the murmur was not heard in the neck. There was no aortic diastolic murmur, and no apical murmurs. The blood pressure was 125/? in both arms. The radial pulses were equal, the femoral pulses absent. A cardiogram showed left ventricular hypertrophy. X-ray and screening showed a prominent ascending aorta, and left ventricular hypertrophy. There was no rib erosion. The patient died at the time of aortography.

Post-mortem findings. Coarctation of the aorta close to the subclavian artery, admitting only a stilette. In addition there was stenosis of the aortic orifice with a bicuspid aortic valve and dilatation of the ascending aorta. There were no other cardiac malformations. No microscopical sections were made.

Final diagnosis. Coarctation of the aorta and congenital bicuspid aortic valve with valvular stenosis.

Case 4. Man, aged 52. Rheumatic fever at 6 years. Increasing effort dyspnœa for a year before admission, culminating in attacks of paroxysmal dyspnœa. On examination the apex beat was in the sixth space at the anterior axillary line. There was a harsh systolic murmur over the præcordium, loudest in the second right interspace, and propagated to the neck. There was also an aortic diastolic murmur and a mitral diastolic murmur. The femoral pulses were strong but collateral circulation apparent. The blood pressure was 290/90 on admission and 190/70 four days later. There were basal crepitations. A cardiogram showed complete heart block and right bundle branch block. On X-ray and screening there was cardiac enlargement, pulmonary congestion, rib notching, and a calcified aortic valve. A Wassermann reaction was negative. The patient responded to treatment for heart failure and was discharged.

Clinical diagnosis. Coarctation of the aorta, calcific aortic stenosis and aortic insufficiency, congestive failure, and ? mitral stenosis.

Case 5 (Dr. Goodwin's case). Man, aged 55 years. He had been aware of heart disease since childhood, but there was no history of rheumatic fever or chorea. He had always noted shortness of breath on exertion, which had increased since pneumonia three years previously. The admission to hospital was due to a further attack of pneumonia. On examination there was a systolic murmur, loudest in the aortic area, and a soft aortic diastolic murmur. There was a moderate systolic murmur and a soft rumbling mid-diastolic murmur at the apex. The blood pressure was 170/60 in both arms, and 110/50 in the legs. A collateral circulation was evident. There were basal crepitations. A cardiogram showed marked left ventricular hypertrophy and intra-cardiac block. On X-ray and screening there was gross left ventricular enlargement, calcification of the aortic valve, and marked dilatation of the ascending aorta and arch. The patient was discharged after treatment for the congestive cardiac failure.

Clinical diagnosis. Coarctation of the aorta, calcific aortic stenosis and incompetence, congestive failure, and ? mitral stenosis.

(*B*) *Cases reported by Other Authors. With Necropsy.* Table I records 24 cases of coarctation accompanied by aortic stenosis as the only valvular lesion. In many of the later cases the microscopic findings have been recorded by the original observers in some detail, and therefore permit an opinion as to the ætiology of the valve lesion; in the earlier cases there was no reason to question the conclusions of the original authors. Only one (Case 25) had an " infantile " rather than an adult type of coarctation.

Without Necropsy. Several cases of this syndrome have been reported, without necropsy control. Grishman *et al.* (1947) report one with aortic stenosis associated with coarctation (their Case 6) and two with other anomalies of the aortic arch (their Cases 2 and 5). Gilbert *et al.* (1950) report the case of a man, aged 52, with the history of an aortic valve lesion at least since the age of thirty: there was no history of rheumatic fever, and the clinical evidence of coarctation was unequivocal; aortic stenosis was diagnosed on the basis of a systolic murmur and thrill, and calcification of the aortic valve was seen radiologically. It is interesting to note that the blood pressure had been high at the age of 12 (160/95), when the patient was refused life insurance; in later life it was recorded as relatively normal in the arms.

Marquis (1954) has recently reported two cases of this syndrome.

Two of our cases are based on clinical findings; each had calcification of the aortic valve on screening.

Discussion

As would be anticipated in coarctation (and also in aortic valvular disease), the males outnumber the females, 4 to 1. This is the proportion that Abbott (1928) found in her 200 cases of coarctation.

The average age at death was 38 years. Reifenstein *et al.* (1947), in their review of 104 autopsied cases of coarctation, found the average age at death to be 35 years. They considered that those patients with complicating valvular disease usually died of congestive failure, and at a later age than those who died of other cardiovascular complications (aortic rupture, cerebral hæmorrhage, and bacterial endocarditis or aortitis). The natural history of these patients appeared to be that of valvular disease rather than of coarctation.

In the present series bicuspid aortic valves were recorded in 20 of 27 cases, an incidence of 74 per cent. This is almost three times the incidence found by Abbott (1928) (25%), and nearly twice that found by Reifenstein *et al.* (42%) in their respective series of cases of coarctation.

In the earlier cases it is not possible to determine whether the bicuspid valves were acquired or congenital. Of the six where adequate microscopical details are given, five had a congenital bicuspid valve. In each case aortic valvular stenosis had developed without any gross or microscopical evidence of rheumatic heart disease. Calcification was recorded in three of these. In one case with adequate microscopical detail calcific aortic stenosis had developed on an acquired bicuspid valve. Calcification was described in 14 cases.

It is generally accepted that it may be difficult to decide, even with detailed microscopical examination, whether rheumatic valvulitis has played a part in producing stenosis of a bicuspid aortic valve. In this respect a report that microscopical evidence of rheumatism was absent was considered particularly significant.

It appears that the association of aortic valvular stenosis with coarctation of the aorta has been largely overlooked. Abbott (1928), in her review of 200 cases, reported only two as having aortic valvular stenosis. A re-examination of the original reports upon which her review was based shows that in a further 11 cases aortic valvular stenosis was described, making an incidence of 6·5 per cent in her series.

A bicuspid aortic valve appears to be about twice as common when aortic valvular stenosis complicates coarctation of the aorta as in a general series of coarctation.

TABLE I

POST-MORTEM CASES OF AORTIC VALVULAR STENOSIS COMPLICATING COARCTATION OF THE AORTA*

Case No.	Author	Sex	Age	Aortic valve		Remarks
				Orifice	Cusps	
1	Craigie, Case 9 (1841)	M	27	Constricted*†	Calcified	Patent ductus arteriosus
2	Peacock, Case 24 (1860)	F	20	Contracted	Bicuspid	
3	Peacock, Case 27 (1860)	M	14	Somewhat narrow	Bicuspid**	
4	Peacock, Case 29 (1860)	M	32	Narrow	Immovable	
5	Barié, Case 58 (1886)	F	19	Very stenosed	Bicuspid	Widely patent ductus arteriosus
6	Barié, Case 78 (1886)	M	65	Considerable stenosis	Bicuspid; calcified	
7	Barié, Case 70 (1886)	M	38	—	Bicuspid	Cusps partially fused
8	Bonnet, Case 14 (1903)	M	25	—	Bicuspid	Anterior cusp rigid and calcified
9	Bonnet, Case 25 (1903)	?	?	Stenosed and incompetent	—	Aortic aneurysm distal to coarctation
10	Fawcett, Case 3 (1905)	F	c. 45	Stenosed	Biscupid	Patent ductus arteriosus
11	Fawcett, Case 10 (1905)	F	34	Stenosed	Bony cretaceous vegetations	Miniature supernumerary cusp ½ in. above valve; bacterial endocarditis
12	Hamilton and Abbott (1920)	M	14	Stenosed and incompetent	Bicuspid**	Sub-aortic stenosis; dissecting aneurysm of aorta: adherent pericardium
13	Abbott (1928) quotes Reinitz (1902)	M	34	Stenosed	Bicuspid**; calcified	
14	Rösler (1928)	M	45	Severe stenosis	Bicuspid	
15	Bode and Knop (1928)‡	M	54	Stenosed	Bicuspid**; calcified	
16	Hein (1931)	M	60	Stenosed	Calcified; " valve incomplete "	
17	Bishop and Trubek (1936)	M	45	Narrow slit	Bicuspid; calcified	Ductus partially obliterated. Microscopical examination suggested inflammatory fusion of aortic cusps
18	Benkwitz and Hunter (1937)	M	37	Stenosis	Bicuspid (probably congenital); calcified	Sub-aortic stenosis; calcified
19	Ingham (1939)	M	50	Severe stenosis	Congenital bicuspid	Microscopically no evidence of inflammation
20	Gitlow and Sommer (1940)	M	45	Severe stenosis	Bicuspid (probably congenital); calcified	Microscopically no evidence of syphilis or rheumatic heart disease
21	Lewis (1945)	M	38	Stenosed	Congenital bicuspid; calcified	Microscopically no evidence of an acquired union between the cusps
22	Clark and Firminger (1949)	M	32	Stenosed	Congenital bicuspid; calcified	Microscopically no evidence of fibrosis or inflammation
23	Jacobson *et al.*, Case 3 (1953)	M	38	Stenosed	Bicuspid**; calcified	
24	Brown (1934)	F	3 days	Severe stenosis	A fibrous diaphragm	Microscopically no endocarditis. Congenital stenosis
25	Present series, Case 1	M	43	Severe stenosis	Calcified	
26	Present series, Case 2	F	18	Slight stenosis	Congenital bicuspid	Microscopically no rheumatic heart disease
27	Present series, Case 3	M	18	Severe stenosis	Bicuspid**	

* In each case the aortic lesion was the only valvular lesion reported. The opinions recorded are those of the original authors. ** Probably congenital.

† Also reported by Peacock (1860, Case 9).

‡ This case was more fully reported by Weber and Knop (1929).

The Ætiology of Aortic Stenosis associated with Coarctation of the Aorta. Brown (1934) described the case of an infant dying three days after birth who had congenital aortic valvular stenosis, coarctation of the aorta, a widely patent ductus arteriosus, and a patent foramen ovale. " There was a fibrous diaphragm at the site of the aortic valves—this was thick and hard and was pierced by a minute opening. The cusps could not be differentiated." There was no evidence that the stenosis of the aortic orifice was due to a fœtal endocarditis. Brown concludes: " A search of the literature has failed to reveal one (*case*) in which orificial stenosis of the aorta was combined with isthmus stenosis." In this he presumably refers to congenital orificial stenosis.

Brown's appears to be the only case in which congenital aortic stenosis was associated with coarctation of the aorta. It is apparent from the above autopsy reports (Table I) that aortic valvular stenosis, when complicating coarctation of the aorta, is an acquired lesion, though this does not exclude the possibility of an underlying malformation. However, Bishop and Trubeck (1934) conclude that the presence of an associated congenital cardiovascular anomaly, such as coarctation of the aorta, cannot be taken as presumptive evidence that the calcified aortic stenosis has developed on a malformed valve. Fawcett (1905), in a review of 18 cases of coarctation, stated that " The constant strain to which the aortic valves are subjected leads in the majority of cases to a chronic inflammatory change with the result that the valves become thickened, or adherent, or the orifice stenosed." He made no mention of bicuspid aortic valves, so that it must be assumed that he was referring to changes in a previously normal valve. Reifenstein *et al.* (1947) concluded that their 11 cases of aortic stenosis associated with coarctation were all attributable to rheumatic heart disease.

The frequent association of coarctation of the aorta with congenital bicuspid aortic valves has already been noted. Abbott reported a further four, and Reifenstein *et al.* three cases of apparently acquired bicuspid valves. Conversely, Lewis and Grant (1923) found that coarctation was the commonest malformation associated with undoubted congenital bicuspid aortic valves. A bicuspid aortic valve occurring with coarctation is, therefore, almost always congenital. Jacobson *et al.* (1953) commented on the rarity of bicuspid valves in this syndrome, but in the present series bicuspid aortic valves were found in 20 of 27 cases (Table II).

TABLE II

INCIDENCE OF BICUSPID AORTIC VALVES IN COARCTATION OF THE AORTA AND AORTIC VALVULAR STENOSIS

Total number of cases of coarctation and aortic stenosis:		27
Bicuspid valve (1) inflammatory	1	
(2) congenital	5	
(3) probably congenital	7	
(4) undetermined	7	
		20
Total number of aortic valves calcified		14
Number of bicuspid aortic valves calcified		9

Bicuspid Aortic Valve as a Basis of Aortic Stenosis. The first worker to remark on the fact that bicuspid semilunar valves are prone to disease appears to have been Paget (1844): " It has never, I believe, been noticed (though there need be no doubt about the fact) that in the majority of cases in which only two valves have been found in the aorta or pulmonary artery, these valves have been diseased and often extremely diseased." Peacock (1851) was among the first to be aware that the high pressure to which the aortic valve is exposed makes it vulnerable to disease. " We know that in after-life the variable pressure of the blood in the arterial system is a fruitful cause of disease in the aortic valves."

These two concepts are of special application in coarctation, where hypertension is almost invariably present and a congenital bicuspid valve common. Peacock also demonstrated clearly that the congenital bicuspid aortic valve could become diseased, and either stenosed or incompetent:

" . . . the defect described (*bicuspid aortic valve*) is shown to be of congenital origin, at least in many instances, by its co-existence with other obvious malformations, and by its occurring in children which survive birth only a short period, and even in fœtuses which have never breathed. . . ." (Peacock, 1886, pp. 131 and 132.)

" The forms of the defect (*bicuspid valve*) now described, though not necessarily interfering with the functions of the heart, do, in a considerable number of cases lay the foundation of disease in after-life." . . . " When the whole of the segments are fused together or when two only are united, the valves not infrequently become the seat of chronic inflammation, by which they are rendered thick and unyielding and often become extensively ossified, thus inducing, first obstruction to the flow of blood from the ventricle into the aorta, and then incompetency." (Peacock, 1886, p. 133.)

Earlier, in his Croonian lectures of 1857, Peacock had expressed views similar to the above, and added: " I believe, however, that when the symptoms and signs of uncomplicated aortic valvular disease manifest themselves in persons who have never had rheumatic fever or other serious illness, . . . we shall generally be correct in assigning its probable production to malformation of the valves." (Peacock, 1857, p. 31.) From this it is clear that Peacock believed that the bicuspid aortic valve frequently becomes stenosed without superimposed rheumatic valvulitis.

Many workers since Peacock have noted that congenital bicuspid valves usually show secondary changes in the adult. Osler (1886) remarked: " The united cusps may have a perfectly normal appearance, but in adults they are almost invariably thickened and the seat of sclerotic or, in some cases, ulcerative changes . . . doubtless the strain on the fused curtains is more severe than upon normal cusps." He commented on the frequency of associated left ventricular hypertrophy.

Lewis and Grant (1923) noted that in congenital bicuspid valves thickenings were " the rule rather than the exception " and occur " as secondary processes in aortic valve margins which fail closely to adjust themselves when the valve shuts." Their investigations included detailed microscopy of bicuspid valves; they regarded these changes as due to faultily functioning valves and not to a rheumatic valvulitis.

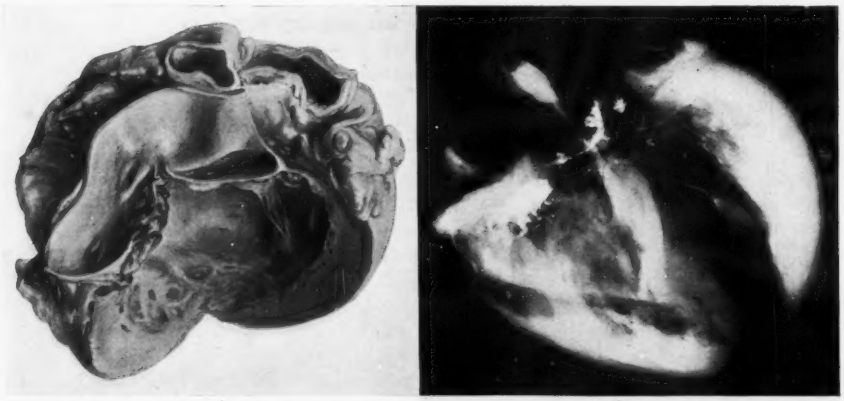
Koletsky (1941), in a study of 18 cases of congenital bicuspid aortic valves concluded, " This anomaly also may pre-dispose to calcific sclerosis," and considered that the association of calcific sclerosis and a congenital bicuspid valve was not very rare. Although he does not discuss aortic stenosis in this communication, in one at least of his cases (Case 13) calcific aortic stenosis was superimposed on a congenital bicuspid aortic valve, and there was no microscopic evidence of rheumatic disease in sections of the heart, valve rings, and valves. He also states: " The inherent tendency of the congenital bicuspid valve to undergo degeneration and fibrosis has been pointed out frequently and is attributed to the fact that abnormally developed cusps are composed of imperfect or defective tissue. The degeneration and fibrosis are undoubtedly accelerated with age, and in older persons, particularly those with an especial tendency to arteriosclerosis, would be prone to lead to the deposition of calcium."

In considering the general problem of calcific aortic stenosis, Karsner and Koletsky (1947) concluded that this lesion is almost always of rheumatic origin. Of 200 cases, only four were not associated with rheumatic stigmata. These conclusions were based essentially on microscopical findings. However, Hall and Anderson (1943) have shown that, if the criteria of Gross *et al.* (1930) are valid for the diagnosis of rheumatic heart disease, the incidence of rheumatic fever is comparable to that of tuberculosis and infantile paralysis. On these grounds the conclusions of Karsner and Koletsky are open to criticism. Kiloh (1950) concluded that a congenital bicuspid valve may well play an important role in the development of calcific aortic stenosis. A similar conclusion is reached by Bailey *et al.* (1954).

Hall and Ichioka (1940) studied the ætiology of 31 cases of nodular calcific aortic stenosis. They divided these cases into 19 with isolated aortic lesions, and 12 with combined aortic and mitral lesions. Using the standard microscopical criteria for rheumatic disease, they concluded that the

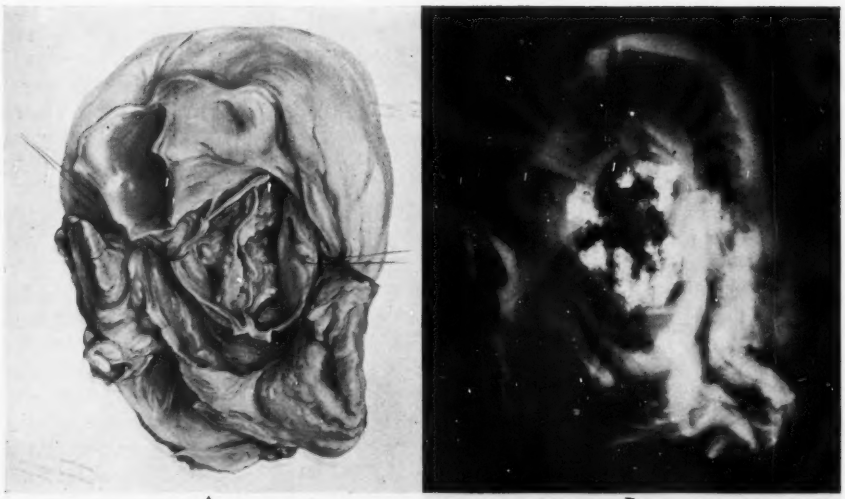
changes in all the cases appear to have a common ætiology and fulfil the criteria generally accepted for chronic rheumatic infections of the heart. The same criticism of these findings may be made as were made of those of Karsner and Koletsky. In addition, it is of interest to note that in 8 of the 19 cases with isolated aortic valve disease bicuspid valves were found, but " strangely none was found in the mixed group."

It is apparent then, that aortic stenosis can develop on a congenital bicuspid valve independently



A B

FIG. 1.—Drawing (A) and X-ray (B) to show calcification in a congenital bicuspid aortic valve which produced aortic stenosis, in a man, aged 60. It is one of Peacock's specimens in St. Thomas's Hospital Museum (No. 1A.1.28), and was originally reported by Bennett (1851), who described the obstruction to blood flow as being due to rigidity of the cusps. [A rudimentary third valve between the other two can be seen in the specimen and drawing; in Peacock (1886) there is an engraving of the specimen (Plate VII, Fig. 3) where it has been exaggerated.]



A B

FIG. 2.—Drawing (A) and X-ray (B), showing calcification in a congenital bicuspid aortic valve in a man, aged 65, with characteristic signs of aortic stenosis. He died suddenly during treatment for left ventricular failure. Note that the obstruction to blood flow is due to rigidity of the cusps; there is no commissural fusion. The left ventricle was markedly hypertrophied. (St. Stephen's Hospital, Case No. 36309.)

of rheumatic inflammation. Reifenstein *et al.* (1947) and Wauchope (1928) have, however, suggested that the congenital bicuspid aortic valve is more prone to rheumatic disease than normally-formed cusps. From the necropsy reports in the present series we suggest that Peacock was correct in concluding that valvular aortic stenosis could arise from degeneration, usually with calcification, in a congenital bicuspid valve. The liability to such changes is increased by the abnormal mechanical stresses of a malformed and malfunctioning valve, and the process hastened by the higher pressures imposed by the coarctation. A similar interpretation of aortic incompetence in coarctation of the aorta with a bicuspid aortic valve is used by Bramwell and King (1942).

Induration and calcification of the cusps, rather than commissural fusion, may be the cause of obstruction at the valve orifice in some cases. Fig. 1 and 2 show the degeneration and calcification that occurred in two congenital bicuspid valves. The first example is of interest in being one of Peacock's own cases from the Museum at St. Thomas's Hospital, and shows extensive calcification in the bicuspid valve of a male, aged 60. The second is from a man of 65 who died of cardiac failure from aortic stenosis. In neither valve was there evidence of an acquired fusion. In both cases left ventricular hypertrophy demonstrated that there had been obstruction to blood flow at the valve. In each the bicuspid valve occurred as an isolated anomaly.

We conclude, therefore, that aortic stenosis is quite common in coarctation of the aorta, and that a congenital bicuspid valve is the common factor.

We suggest that these conclusions may have a wider implication in accounting for some cases of isolated calcific stenosis of undetermined ætiology. It is possible that some of those patients whose bicuspid aortic valves are not revealed by subacute bacterial endocarditis may present in old age with the signs of aortic stenosis as the first overt evidence of this malformation. Support is lent to this conclusion by the fact that, in old age, aortic stenosis is commoner in men than women.

Often the calcified aortic valve can be seen to be bicuspid, but if the calcification and destruction of the valve are far advanced, as is so frequently the case, a correct morphological interpretation may be impossible and the histological picture confused.

Note on Diagnosis. The clinical diagnosis of aortic stenosis in the presence of coarctation is important now that surgical treatment is possible. Uncomplicated coarctation of the aorta may produce systolic murmurs sufficiently loud to cause a thrill (Reifenstein *et al.*, 1947), and the thrill may disappear after a successful resection of the coarctation (Goodwin, 1954). If the murmur is obviously louder to the right of the sternum than to the left, the possibility of aortic valvular stenosis should be considered.

If there are typical enlarged collateral blood vessels, and a weak and delayed or absent femoral pulse, the finding of a normal blood pressure in the arms is extremely suggestive of co-existing aortic stenosis. Bishop and Trubeck (1936) report the finding of a blood pressure of 110/70 in the upper extremities in a man of 45 with this combination (Case 18, Table I). In Cases 15 and 27 the blood pressure in the arms was also normal. In the clinical case of Gilbert *et al.* (1950) already noted, the blood pressure in the arms had been raised at the age of 12 (165/95), but was normal 40 years later.

The brachial arterial pressure pulse may be helpful if it shows prolonged systolic ejection or anacrotism, as suggested by Grishman *et al.* (1947). The differentiation of valvular from subvalvular stenosis is impossible, though calcification visible on X-ray is more suggestive of the former. Evidence of left ventricular hypertrophy on X-ray screening, or from the electrocardiogram is to be expected more frequently than in isolated coarctation.

Summary and Conclusions

Five cases of aortic valvular stenosis combined with coarctation of the aorta are described. In three there was necropsy control, and in the other two radiological evidence of calcification of the aortic valve. A further 24 similar reported cases with necropsy control are reviewed. A re-examination of the original reports upon which Abbott's (1928) review of 200 cases of coarctation were based shows the incidence of aortic valvular stenosis to be 6·5 per cent.

Of the 27 cases with necropsies, 20 had a bicuspid aortic valve. In 5 of the 6 where microscopy

was adequate, the absence of rheumatic stigmata was taken to indicate that the bicuspid valve was congenital and the stenosis not rheumatic. In a further 7 the original authors considered that the bicuspid valve was congenital, while only one was proved on microscopy to have arisen from fusion of two of three cusps.

It is concluded that Peacock's suggestion that degeneration in a congenital bicuspid valve can lead to aortic stenosis is correct. The frequency of congenital bicuspid valve in association with coarctation, its abnormal structure, and the higher pressures to which in coarctation the aortic valve is exposed, are considered to be the factors responsible for the development of aortic stenosis with coarctation.

It is suggested that the importance of degeneration of the congenital bicuspid valve as a cause of isolated calcific aortic stenosis has not received sufficient attention. This is attributed to the difficulty of morphological interpretation when the deformity and calcification are far advanced.

The clinical features of the syndrome are briefly discussed.

We are grateful to Dr. J. F. Goodwin for putting at our disposal the records of Cases 2 and 4, and to Dr. Jean Bret of Lyons for the details of Case 3; to Dr. Raymond Daley for the specimen shown in Fig. 2; to Dr. A. C. Dornhorst for helpful criticism; to Miss Joan Dewe for the illustrations and to Mr. A. L. Wooding for their reproduction.

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THROMBOSIS OF THE MAIN PULMONARY ARTERIES*

BY

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The clinical and pathological features of massive thrombosis of the pulmonary arteries have been well documented in recent years but the condition has seldom been recognized during life. In many cases clinical diagnosis is unlikely because the thrombosis is terminal or insidious, in patients already seriously ill with cardiac or pulmonary disease, and merely hastens the end by increasing the load on the right ventricle. However, thrombus may be present in the main pulmonary arteries for a period of weeks or even years, until sudden fresh thrombosis completes the occlusion and proves fatal, so that the condition cannot be considered purely terminal (Brenner, 1935; and Savacool and Charr, 1941). Furthermore, a number of reports have demonstrated that thrombosis of main pulmonary arteries may, on rare occasions, initiate chronic right heart failure, closely resembling chronic cor pulmonale from the more usual causes. Von Jürgensen (1908) described a case showing complete obstruction of the pulmonary trunk with " mainly old firm clot "; he stated that a large portion of the lumen could be " rendered impermeable " without causing death. Experimentally this suggestion was confirmed by the demonstration in dogs that the main pulmonary artery could be compressed gradually until 60 per cent of its lumen was obliterated, without a fall in systemic blood pressure, and that death did not occur until roughly 90 per cent occlusion was reached (Gibbon *et al.*, 1932).

Posselt (1909) could find only three examples of complete occlusion of the main pulmonary artery or its branches. Ljungdahl (1928), Barnes and Yater (1929), Jump and Baumann (1929) and Means and Mallory (1932) described patients showing chronic right heart failure; in each case organized or organizing thrombus occluded the main pulmonary artery or its branches. The case of Means and Mallory showed evidence of collateral circulation to the lungs via hypertrophied bronchial and other mediastinal arteries. Brenner (1935) demonstrated the relative frequency of thrombosis of smaller arteries, but he could only report six examples of organized thrombus of the main pulmonary artery; involvement of primary branches was commoner, but in either situation symptoms attributable to the occlusion were rare. Fowler (1934), Mallory (1940), and Covey (1943) described patients showing a chronic course, characterized by dyspnœa, cyanosis, præcordial distress, and heart failure. In each of these patients severe paroxysmal cough sometimes associated with deepening cyanosis was a noteworthy feature. Harvey and Hogg (1946) discussed the condition in children, citing fourteen reported cases and adding one of their own. Carrol (1950) presented five new cases in two of which venous catheterization of the heart revealed elevated right ventricular pressures. In one patient thoracotomy was undertaken after a diagnosis of obstruction of the left pulmonary artery had been made and a biopsy of the artery revealed organized thrombosis. This author emphasized again the occurrence of chronic right heart failure and noted the frequent finding of right ventricular hypertrophy patterns in the electrocardiogram. Hanelin and Eyler

* Part of this work was done while one of us (O. M.) was a Fellow in Medicine (Cardiology) of the University of Southern California, supported by the San Diego Heart Association.

(1951) presented five patients and established the criteria on which a radiological diagnosis might be made.

It is the purpose of this paper to determine the incidence of the condition and to present and comment upon the clinical and pathological features of nine examples.

Present Material and Classification. Nine patients were studied of whom six were seen in Los Angeles and three in Leeds. The patients have been separated on clinical grounds into a group of four showing chronic right heart failure (Group I) and a second group of five with an acute or subacute course (Group II).

Incidence. The incidence of the condition over a twenty-year period (1930–1949) was determined from a study of the extensive autopsy records of the Los Angeles County Hospital. The results are shown in Table I which also includes the figures for frank pulmonary embolism for comparison. Evidently the condition under discussion is quite rare, occurring approximately once in five thousand autopsies in a large general hospital.

TABLE I

INCIDENCE OF PULMONARY EMBOLISM AND ARTERIAL THROMBOSIS

	Total autopsies 1930–39	Pulmonary artery thrombosis (all size arteries)	Thrombosis of major pulmonary arteries as cause of death	Pulmonary embolism
Total	35,003	361	7	1469
Percentage	100	1·03	0·02	4·2

GROUP I. PATIENTS WITH CHRONIC RIGHT HEART FAILURE

Case 1. B. W. was a widow, aged 59 years, at the time of her death. In March, 1949, she was admitted to hospital with an appendix abscess which resolved without surgical intervention. At that time the cardiovascular system was clinically normal. In June, 1949, she suffered an attack of thrombophlebitis of the left leg. During the course of this attack she noticed the onset of shortness of breath on effort. In February, 1950, the right leg became swollen and tender and the dyspnœa increased in severity. She was found to have a right femoral thrombosis. There was no cardiac enlargement, but a soft apical systolic murmur and a blood pressure (B.P.) of 180/110 mm. In September, 1950, she was admitted to hospital as an urgent case with severe breathlessness, orthopnœa, and painless swelling of the legs.

She was orthopnœic with cyanosis of the lips and fingers, but without finger clubbing. The venous pressure was raised with a strong auricular systolic wave in the external jugular veins. The pulse rate was 100 a minute and regular. B.P. 160/110 mm. Hg. There was gross œdema of the legs and a sacral pad and the liver was enlarged and tender. The heart was clinically enlarged with a parasternal heave and a pulmonary diastolic shock. There was a systolic thrill maximal over the sternal end of the third left rib. The second sound in the pulmonary area (PII) was markedly accentuated and split and a loud systolic murmur was audible, loudest in the third left intercostal space.

An electrocardiogram showed right ventricular hypertrophy. The skiagram showed cardiac enlargement with fullness of the pulmonary artery segment. The lung fields were relatively clear (Fig. 1).

She responded moderately well to treatment for her heart failure and was discharged in November, free of œdema, able to walk 100 yds. but still cyanotic. Her condition remained relatively stationary until February, 1951, when she had an attack of " influenza " shortly after which she was re-admitted to hospital with severe breathlessness, cyanosis, and œdema. The clinical findings were as before. Progress was very slow but after slight improvement, dyspnœa and cyanosis suddenly increased and she died within the next few minutes.

Post-mortem Examination. Heart. The right ventricle was hypertrophied and dilated. Left ventricle appeared normal. Coronary arteries showed minimal atheroma. There was no congenital nor acquired valvular disease.

Pulmonary Arteries. Organized antemortem thrombus straddled the bifurcation of the main pulmonary artery, extending 3 cm. into the right branch and along the whole length of the left into the hilum of the lung. The clot extended several centimetres down into the main trunk. Overall the clot occluded about three-

quarters of the lumen of the vessels (Fig. 3 and 4). The lungs showed no gross abnormalities. In the peripheral venous system the right femoral and popliteal system contained organized and fresh thrombus.

Histology. The pulmonary artery clot consisted of old thrombus firmly attached to the walls of the arteries and showing dense organization in its deeper layers.

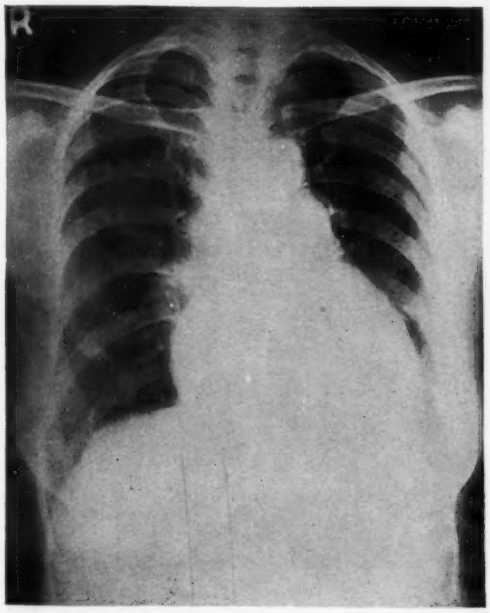

FIG. 1.—Case 1. Skiagram of September, 1950.

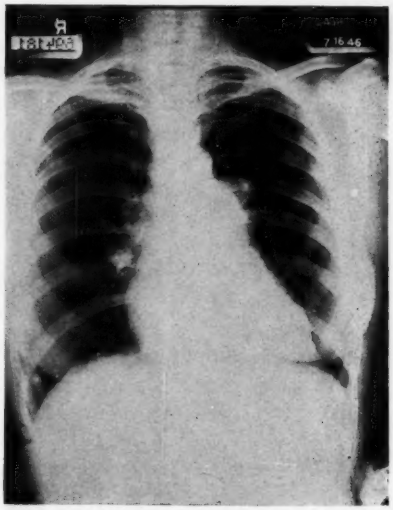

FIG. 2.—Case 2. Skiagram of July, 1946. The shadow adjacent to the pulmonary artery segment was suspected to be a pulmonary neoplasm.

Comment. At the time of this patient's admission to hospital with heart failure her previous history and physical findings were not known and she was thought to be suffering from congenital heart disease, either a ventricular or atrial septal defect. The right-sided enlargement of the heart, thrill, and split second sound were in keeping with either diagnosis. The final clinical diagnosis was ventricular septal defect with associated pulmonary hypertension.

Necropsy revealed only massive organized thrombus of the major pulmonary arteries without evidence of underlying disease. There is no evidence that the thrombosis was secondary to primary pulmonary vascular sclerosis and clinical signs of pulmonary hypertension were not present in February, 1950, yet in September, 1950, she was in severe right heart failure. It seems likely that the illness started early in 1950 and that the thrombus propagated rapidly prior to her admission in September. Severe heart failure from obstruction lasted in all six months. Despite the absence of a clear history we believe that the attack of thrombophlebitis in 1949 was responsible for pulmonary embolism which was followed by extension of thrombus and increasing obstruction of the main pulmonary arteries.

Case 2. E. M. B. was a woman, aged 48 years at the time of her death. She first attended as an out-patient in June, 1946, with severe non-productive cough, dyspnœa, pain in the left thigh and calf and in the right side of the chest. There was œdema of both legs especially in the left leg, which was cyanosed with dilated superficial veins. The heart was not enlarged but PII was loud and a pulmonary systolic murmur was audible. It was noted at this time that she became quite dyspnœic with the effort of combing her hair. She was admitted to the wards and with rest her condition improved. A skiagram taken at this time is shown in Fig. 2. An electrocardiogram showed right ventricular hypertrophy. One month later she was re-admitted with cough, breathlessness, and a return of swelling of the left leg and thigh with associated tenderness and thickening of the femoral vein. The arm-to-tongue circulation time

FIG. 3.—Case 1. Heart showing right ventricular hypertrophy and a thrombus in the pulmonary arteries.

FIG. 4.—Case 1. Lung root showing a dense thrombus occluding the pulmonary artery.

was prolonged to 28 sec. and the venous pressure was markedly raised. The blood pressure was 150/80 mm. She was discharged improved within a few weeks. She was admitted for the third time in November, 1947. She presented a picture of right heart failure with high venous pressure, cyanosis, and a loud systolic murmur and thrill over the body of the heart. It was considered that she might have a ventricular septal defect and pulmonary hypertension. A skiagram at this time showed an apparent mass in the region of the left pulmonary artery and a diagnosis of neoplasm of the lung was considered. In early December she had evidence of consolidation in the left upper lobe with a slight fever; in late December she experienced acute right pleuritic pain and a friction rub was heard over the right lung base. With each of these two incidents cyanosis increased considerably. In January, 1948, cardiac catheterization was attempted but demonstrated only a raised right atrial pressure. She was discharged only to be readmitted for the last time in April, 1948. The symptoms were as before but in addition she had constant dull boring substernal pain from which no relief could be obtained. She was feeling very weak and dizzy and the œdema of the legs had become extreme.

Physical examination showed her to be markedly orthopnœic, distressed, and cyanotic. There was distension and vigorous systolic pulsation of the deep veins of the neck. Grade II finger clubbing was present. The pulse was regular at 46 a minute. The blood pressure was 105/70 mm. The heart was enlarged. A changing first heart sound suggested complete heart block. A rough systolic murmur was heard over the body and base of the heart and was accompanied by a thrill. The liver was enlarged and tender. There were no râles or crepitations in the lungs. The skin was cold and clammy and she died suddenly on the evening of the day of admission.

Post-mortem Examination. Heart. Greatly enlarged with dilatation of the right chambers. Weight 480 g. Left ventricular wall 10–12 mm. thick. Right ventricular wall 8–9 mm. thick. Coronary arteries thin-walled and patent. There was a patent foramen ovale which could be opened up to a diameter of about 2·5 mm.

Pulmonary arteries. Firmly adherent dense thrombus was found beginning just below the bifurcation of the pulmonary artery and especially attached to the right main branch which was completely occluded.

The clot extended into the branches to all three lobes. Some of the vessels distal to the thrombus were still patent although numerous small branches showed dense firm fibrous strands in their lumina consistent with old organized thrombi; a few of these vessels had been recanalized. The left lung was similarly affected with the exception that the main artery on the left was partially patent.

Lungs. Generally, the lung parenchyma, tracheobronchial tree, and lymph nodes showed nothing of note with the exception of a dense scar in the left lower lobe extending to the pleural surface.

Peripheral veins. The left femoral system contained old organized thrombus.

Histology. The pleura and lung showed scattered atypical tubercles of sarcoidosis. Sections of mediastinal lymph nodes showed the characteristic changes of Boeck's sarcoid. The larger pulmonary vessels showed evidence of both old organized thrombus and relatively recent clot.

Comment. This woman had an illness of two-years duration with four admissions to hospital. The cause of her severe symptoms and heart failure was not suspected. It seems probable that she suffered from occlusion of the pulmonary vessels dating from pulmonary embolism occurring during the course of thrombophlebitis or phlebothrombosis in June, 1946. The extensive clot found at autopsy must have resulted from propagation of thrombus around the original embolus. The patent foramen ovale was only 2·5 mm. in diameter and flap-like and could not be classed as an atrial septal defect. It is likely that part of the venous return may have passed from right to left through the foramen ovale in the face of the pulmonary arterial obstruction.

It may be postulated that the thrombus arose *in situ* in lungs affected by sarcoidosis but the scattered and relatively slight involvement and the history makes this less likely than that the condition was secondary to pulmonary embolism.

Case 3. N. L. H. was a woman, aged 60 years at the time of her death. She was well until 1942 when she had a hysterectomy for fibroids. Two weeks after the operation she suffered sudden onset of severe retrosternal pain radiating into the right arm associated with breathlessness. She was told she had had a heart attack and was kept in bed for eight weeks. Since that time she had been breathless, severely on exertion and slightly even at rest. Positive Wassermann and Kahn reactions were noted in 1942, and in 1944 she had a course of intramuscular injections. In 1946 her doctor prescribed digitalis because of severe breathlessness and swelling of the ankles. She was admitted to hospital in April, 1947, because of digitalis intoxication. At this time she was dyspnœic and slightly cyanotic, but free of œdema. There was venous hypertension, moderate cardiac enlargement, gallop rhythm, and accentuation of PII. The blood pressure was 150/90 mm. A cardiogram showed right axis deviation and clockwise rotation. A skiagram showed cardiac enlargement with a density at the right base. The Wassermann and Kahn reactions were positive.

After her discharge from hospital she remained virtually bedridden. A skiagram taken in February, 1948, is shown in Fig. 5. She was finally admitted in September, 1948. She was extremely ill and cyanotic with slight finger clubbing, cardiac enlargement, gallop rhythm, and an accentuated pulmonary second sound. There were no murmurs. An electrocardiogram showed bigeminy due to auricular premature beats and right ventricular enlargement. She lapsed into coma and died within a few days of admission.

Post-mortem Examination. *Heart*. Weight 450 g. The right heart was enlarged and dilated. The right ventricle measured 12 mm. in thickness and the left ventricle 13 mm. The cardiac valves and coronary arteries appeared healthy.

Pulmonary arteries. Contained within the main pulmonary artery was an organized thrombus approximately 3 cm. in diameter which extended upwards and completely occluded the left pulmonary artery extending into its primary branches (Fig. 6). The pulmonary vascular tree throughout both lungs appeared dilated and degenerative changes were present throughout.

Lungs. The right lung showed multiple ante-mortem clots throughout the entire arterial tree. The right upper lobe appeared to be completely infarcted. Two small infarcts were present in the right lower lobe.

Histology. Main pulmonary artery. The intima was covered by densely organized thrombus. The media and adventitia showed much scarring and moderately heavy round cell infiltration. There was marked fibrosis with round cell and plasma cell infiltration in the perivascular spaces. The changes were suggestive but not diagnostic of a syphilitic origin.

Arterioles showed fibrous thickening and in places round cell infiltration. The small pulmonary arteries were severely involved by arteriosclerotic changes. The aorta showed slight scarring in the perivascular spaces of the media and much arteriosclerosis of the intima.

Comment. This woman suffered from chronic right heart failure and at death showed densely organized thrombotic occlusion of the main and left pulmonary arteries. She was a known syphilitic and the pathological changes within the pulmonary vessels were suggestive of syphilis. It seems likely that the heart failure resulted from the pulmonary vascular sclerosis complicated by thrombosis *in situ*. Six years before death, however, she suffered an episode suggesting pulmonary embolism. It is possible that the thrombus originated from the pulmonary embolus and was not a true autochthonous thrombus.

FIG. 5.—Case 5. Skiagram of May, 1948.

FIG. 6.—Case 3. Heart and pulmonary artery showing a massive pulmonary artery thrombus.

Case 4. B. G. was a man, aged 40 at the time of his death. He was first admitted to hospital in September, 1947. Several months before he had had left-sided pneumonia. Since that time he had experienced early morning cough and breathlessness on exertion. A systolic murmur over the cardiac base, enlargement of the heart with a prominent pulmonary artery segment, and right axis deviation in the cardiogram led to a diagnosis of congenital pulmonary stenosis. In 1948 and 1949 he was seen in the out-patient clinic; breathlessness was troublesome and for a period in 1949 he had œdema of the legs and spent three months in bed at home. In 1950 the diagnosis was considered to rest between atrial septal defect and primary pulmonary hypertension. He was re-admitted in January, 1953. He was well built without cyanosis or finger clubbing. The pulse was regular, and the blood pressure 95/80 mm. in both arms. The neck veins were distended and noted to be pulsating vigorously. The heart was enlarged and the only auscultatory sign of note was a very loud and split PII. The liver was enlarged and slight œdema was present. While in hospital he had an attack of severe epigastric pain lasting fourteen hours, and on another occasion left pleuritic pain. He was discharged in April still incapacitated by dyspnœa on the slightest exertion. He re-entered hospital for the last time in November, 1953, with severe congestive heart failure and pain across the lower chest and epigastrium. He was now cyanotic, orthopnœic, and in severe right heart failure with gallop rhythm. The cardiogram showed right ventricular enlargement. Skiagrams taken at this time are shown in Fig. 7 and 8. He died within a few days of admission with intractable heart failure.

Post-mortem Examination. Heart. Weight 700 g. There was enormous enlargement due to massive hypertrophy of the right atrium and ventricle. There was no evidence of any congenital anomaly.

Pulmonary arteries. The first 3 cm. of the pulmonary trunk appeared practically normal though somewhat dilated. Distal to this point the trunk and both pulmonary arteries were enormously distended by laminated thrombus of some age, which was firmly adherent to three-quarters of the lumen and organized in

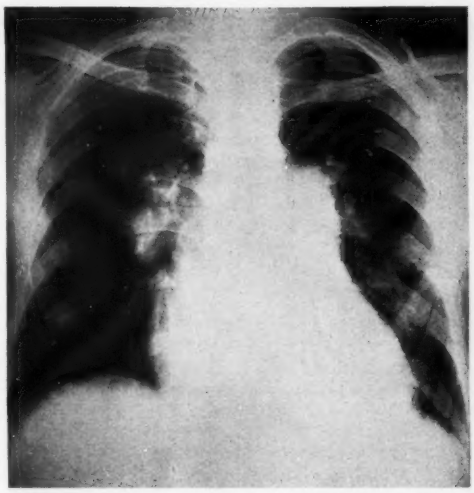

FIG. 7.—Case 4. Skiagram of November, 1953.

FIG. 8.—Case 4. Left lateral skiagram of November, 1953, demonstrating the dense left pulmonary artery with an irregular end.

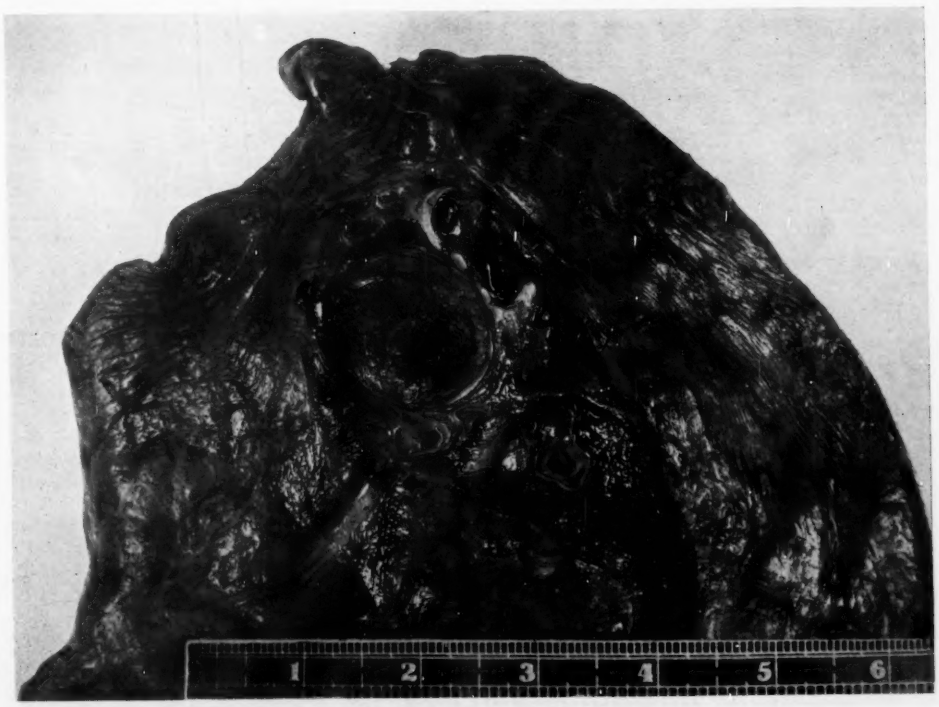

FIG. 9.—Case 4. Lung root showing the pulmonary artery occluded and distended with firm thrombus.

its deeper layers. The thrombus extended for some distance into the branches of the pulmonary arteries in both lungs. There was only a small cleft between the thrombus and the wall of the pulmonary trunk (Fig. 9). The lungs showed several small, fairly recent infarcts in all lobes of both lungs. There was no evidence of pulmonary disease. The leg veins were free of thrombus.

Histology. The majority of the arterioles examined showed concentric medial hypertrophy and narrowing of their lumina. In a few the thickened muscle coat was also partially fibrotic. There was also thickening and condensation of the adventitia. In most of the vessels so affected the lumen was concentrically narrowed and in some obliterated; occasionally the lumen was irregular due to the protrusion of small pads or nodules of muscular tissue from the media.

Comment. This man had progressive right heart failure which lasted about six years. The disproportionate enlargement of the right side of the heart and the absence of any congenital cardiac anomaly indicated that the heart failure was due to obstruction of the pulmonary circulation. Histological examination showed the primary condition to be one of sclerosis of the pulmonary vessels, complicated at a later stage by obliterating thrombosis of the trunk and larger branches of the pulmonary artery.

Group II. Patients with Acute and Subacute Failure

Case 5. T. A. M. was a man, aged 78 years. He was admitted to hospital in 1949 as an emergency. For several months he had had severe breathlessness on effort which had become extremely acute two days before admission. He presented acute dyspnœa accompanied by moderate cyanosis and restlessness. His skin was cold and dry. There was much venous distension. The heart rate was 130. There was cardiac enlargement and a gallop rhythm. The blood pressure was 110/70 mm. He made no response to treatment and died within six hours of admission.

Post-mortem Examination. Heart. Weight 370 g. Moderate right ventricular hypertrophy and dilatation. The right ventricular wall measured 6–8 mm. and the left 12–14 mm.

Pulmonary arteries. The main vessel was moderately dilated and measured 10 cm. in circumference. At the bifurcation there was a relatively recent thrombus, reddish with scattered white lines in it, extending 10 cm. into the left pulmonary artery. It was moderately adherent to underlying, old, well-laminated, brownish-white thrombus densely adherent to the pulmonary artery at the bifurcation. Old thrombus extended about 5 cm. into the left pulmonary artery and approximately 4 cm. into the right. The combined clot occluded approximately one-half of the lumen of the right and left pulmonary arteries. The lungs showed no emphysema or gross disease.

Peripheral veins. Old thrombus was present in the deep femoral system on the right side.

Histology. The pulmonary artery wall was thicker than normal and densely adherent to it was the thrombus, showing advanced organization; attached to this was recent thrombus showing lines of Zahn. The smaller arteries and arterioles showed no pathological changes.

Comment. Death in this patient occurred from acute obstruction of the pulmonary circulation due to the deposition of recent clot upon old adherent thrombus. There was no clinical indication of the cause of the initial thrombosis and the autopsy revealed no pulmonary or cardiac disease.

Case 6. W. B. M. was a 52-year-old coloured man who entered hospital for increasing dyspnœa over the preceding three weeks. He had suffered from breathlessness on effort for about three years. Three hours before admission he experienced pain in the left shoulder. Examination showed moderate dyspnœa and orthopnœa. No definite abnormality could be made out in the lungs or heart but the blood pressure was 235/130 mm. A few hours after entering he developed pain in the abdomen with sweating and pallor and died after passing a bloody stool.

Post-mortem Examination. Heart. Weight 500 g. Both the right and left ventricular walls measured about 12 mm. in thickness. Coronary arteries were patent and showed very little atheroma. The pulmonary arteries generally appeared thickened and showed moderate atheroma. An old well organized thrombus markedly adherent to the vessel wall arose 2 cm. proximal to the bifurcation of the main pulmonary artery. It filled the major portion of the lumen of both the main branches. The thrombus on the right measured 2–3 cm. in diameter, the remaining lumen forming a small crescent about one-half this size. On the left about one-half of the lumen was occluded. Overlying the deeper organized clot was more recent thrombus. The lungs were equal in size and crepitant.

Case 7. W. F. C. was a man admitted to hospital at the age of 41 years with dyspnœa and hæmoptosis. A cavity was found at the apex of the left lower lobe but tubercle bacilli were not isolated. Breathlessness continued and he was re-admitted six months later with a severe exacerbation of the dyspnœa, tightness in the chest, and abdominal pain which had been present for two weeks.

He was dyspnœic and cyanotic with a cold moist skin. There was tachycardia, cardiac enlargement and a triple rhythm at the apex. The lungs showed scanty crepitations at the bases. The blood pressure was unobtainable and the venous pressure measured 320 mm. water in a brachial vein. He died shortly after admission.

Post-mortem Examination. Heart. Weight 450 g. The right ventricular wall measured 8 mm., the left ventricular wall 14 mm. in thickness. The myocardium and valves appeared normal. The coronary arteries showed minimal atheroma.

Pulmonary arteries. The main pulmonary artery was occluded by a red thrombus beginning 2 cm. beyond the valve and extending out as far as the smaller branches in both lungs. Superficially the thrombus was red and soft and showed typical laminæ, but deeper it was tough, yellow and adherent to the arterial wall. The wall of the main pulmonary artery was not noticeably thickened but in most of the secondary branches were thickened yellowish atheromatous plaques. The lungs were light and fluffy. The apex of the left lower lobe contained a cystic cavity measuring 3 cm. in diameter.

Peripheral veins. The left common iliac vein was obstructed by a tough fibrous plug.

Case 8. J. W. K. entered hospital with a provisional diagnosis of cerebral embolism from rheumatic heart disease. His relatives reported that he had been breathless and had complained of pressure in his chest and swelling of his ankles for about four weeks. The day before admission he had become drowsy and then rapidly comatose.

He was a 55-year-old man, comatose and cyanotic, with ankle œdema. Distension of neck and arm veins was evident. There was a loudly accentuated PII. He became more cyanotic and died within a few hours of admission.

Post-mortem Examination. Heart. Weight 670 g. The right ventricular wall measured 7 mm. in thickness and the left 14 mm. The valves showed only a slight and incomplete degree of adhesion of the aortic valve cusps. The coronary arteries were patent throughout.

Pulmonary arteries. In the pulmonary artery, beginning at the bifurcation, was a massive thrombus which was adherent and whose deeper layers were pale and organized. The lungs showed no gross abnormality. The brain and cerebral vessels showed no gross abnormality.

Histology. There were some hyaline changes in the pulmonary artery contiguous upon organized thrombus. Unorganized clot had been laid down on the surface. The smaller vessels showed no significant changes. The lung parenchyma was emphysematous.

Comment. As in Case 5, Cases 6, 7, and 8 showed extensive recent clot superimposed on deep organized thrombus. In each patient symptoms had progressed for several weeks, finally necessitating admission to hospital in extremis. The clinical picture on admission in Cases 5 and 7 closely resembled that seen in massive pulmonary embolism. None of the cases had a history suggesting embolism in the past and no obvious cause for the original thrombosis or its preterminal extension could be found.

Case 9. M. H. was a woman, aged 74 years, who lived alone and who was found ill in bed by a neighbour. She had been in bed for three weeks with weakness, breathlessness, and blueness and pain in the tip of the nose. On examination she was thin, dehydrated, and mentally disorientated. The neck veins were distended, the hands were cold, and the nose showed early gangrene. The heart was clinically enlarged. The blood pressure was unobtainable and the pulse impalpable. A sacral pad of œdema was present and the liver was enlarged. She died without a diagnosis having been made.

Post-mortem Examination. Heart. Weight 400 g. Great dilatation of the right side. Mild coronary atheroma was present.

Pulmonary arteries. All the branches of the pulmonary arteries were filled with firm antemortem thrombus of some duration. The thrombus started at the commencement of the two main branches of the pulmonary trunk and extended to the periphery, filling all the visible branches. The lungs appeared small. There were bilateral, blood stained, pleural effusions.

The only other significant findings were a small chronic duodenal ulcer and cystitis.

Comment. This woman survived three weeks with propagating pulmonary artery thrombus which almost certainly arose *in situ*. Dehydration may have played an important part in initiating the thrombosis. The marked peripheral vaso-constriction leading to gangrene of the tip of the nose was a striking manifestation in this case.

Clinical Features

Group I. In Cases 1 and 2 the whole cardiac illness can reasonably be attributed to pulmonary artery thrombosis, while in Cases 3 and 4 right heart disease due to pulmonary vascular sclerosis. probably existed before the onset of the thrombosis. The clinical features were those of chronic and intractable right heart failure without evidence of pulmonary parenchymal disease or pulmonary congestion yet with severe breathlessness on slight effort and orthopnœa. Cough was a troublesome symptom in Cases 2 and 4 and in both severe retrosternal and epigastric pain occurred in the later stages of the illness. This latter symptom has been discussed by Middleton (1943). Cyanosis and

finger clubbing were late developments. No direct evidence as to whether the cyanosis was central or peripheral was obtained, but a right-to-left shunt through the patent foramen ovale in Case 2, in which a raised right atrial pressure was demonstrated, seems probable.

Physical examination was characterized by a raised venous pressure, enlargement of the heart, triple rhythm, accentuation of the second sound in the pulmonary area, and basal systolic murmurs. In Cases 1 and 2 loud rough systolic murmurs accompanied by a thrill were noted, leading in both to the diagnosis of congenital heart disease. The occurrence of cardiac murmurs has been mentioned occasionally in relation to pulmonary artery thrombosis (Posselt, 1909; Covey, 1943; Carrol, 1950; and Dimond and Jones, 1953). The arterial blood pressure was well sustained until the terminal stages of the illness.

Electrocardiograms were taken at various stages of the illness and always showed right ventricular enlargement patterns. The P pulmonale was not a feature, being seen only in Case 4 in the right præcordial leads. Complete heart block was recorded terminally in Case 2; Case 3 showed bigeminy due to auricular premature beats during her last admission and Case 4 had a prolonged P–R interval at least two years before his death.

Radiological examination was carried out in these cases and although the correct diagnosis was not considered during life, a review of the films showed that the features described by Hanelin and Eyler (1951) were present (Fig. 1, 4, 5, 7, and 8). These features are as follows.

(1) Enlargement of the right heart.
(2) Dilatation of the affected pulmonary artery proximal to the block.
(3) Enlargement and alteration in the contour of the vessels at the level of the thrombus.
(4) Decrease in the calibre of the vessels distal to the thrombus with increased radiotranslucency in the corresponding areas.

Group II. Cases 5, 6, and 7 were admitted with acute heart failure after a few weeks to a few months of increasing breathlessness on exertion. The clinical picture in Cases 5 and 7 closely resembled that seen in acute massive pulmonary embolism, with venous hypertension, gallop rhythm, tachycardia, cyanosis, and cold extremities. Case 8 had complained of increasing dyspnœa, chest oppression, and swelling of the ankles for about a month prior to admission and was admitted in coma. Case 9 followed a subacute course over a period of several weeks, characterized by severe peripheral circulatory insufficiency associated with cardiac failure culminating in early gangrene of the extremities.

Pathological Features

The essential pathological findings are set out in Table II. In all cases the main pulmonary trunk or the bifurcation was affected by the thrombosis with extension into one or other or both branches. No predeliction for one or other branch of the pulmonary artery was seen. In all the cases firm, old clot was found adherent to the main trunk or the bifurcation and in general more recent clot had been added. Case 9 differed somewhat in showing uniform continuous thrombus throughout the smaller and larger branches of the pulmonary artery. With the exception of this patient the pathological features were essentially similar in all cases irrespective of the clinical group into which the patients were placed.

Gross parenchymal disease of the lungs was not seen. Significant disease of the large pulmonary arteries was found in only three cases (Table II). Arteriolar disease, possibly syphilitic, was found in Case 3, and diffuse arteriolar sclerosis of unknown origin in Case 4. Valvular or arteriosclerotic heart disease was not present and only Case 6 with severe hypertension had heart disease that might have altered the clinical picture produced by obstruction in the pulmonary circulation. All the cases showed hypertrophy or dilatation of the right side of the heart consequent on the pulmonary vascular obstruction and could be considered, from a pathological standpoint, examples of chronic or subacute cor pulmonale.

A series of cases of this type raises the question whether pulmonary embolism with subsequent

TABLE II
PATHOLOGICAL FINDINGS

Case No.	Age and sex	Pulmonary arteries	Heart	Other significant findings
1	59 F	Organized thrombus main and both branches occluded 3/4 lumen	420 g. R.V. hypertrophy and dilatation	Organized and fresh thrombus right femoral venous system
2	48 F	Dense thrombus main and both branches	480 g. R.V. hypertrophy. Patent foramen ovale	Histologically Boecks sarcoid of lung and tracheo bronchial lymph nodes. Old thrombus, left femoral system
3	60 F	Organized thrombus main and completely occluding left	450 g. R. V. hypertrophy. Mural thrombus right ventricle	Possibly syphilitic pulmonary arteritis. Tuberculous cavity left apex. Infarcts L and R upper lobes
4	40 M	Trunk and both branches distended with laminated clot of some age	700 g. Massive R.V. hypertrophy	Histologically primary pulmonary vascular sclerosis
5	78 M	Old well-laminated clot adherent to bifurcation. Recent clot superimposed	370 g. R.V. hypertrophy and dilatation	Old thrombus in right deep femoral veins
6	52 M	Old thrombus main and both branches	500 g. R.V. hypertrophy and dilatation	Pulmonary artery atheroma
7	41 M	Deep tough thrombus adherent to wall main branch. Superficial recent clot	450 g.	Tough fibrous plug in left common iliac vein. Atheroma secondary branches pulmonary artery
8	55 M	Thrombus across bifurcation	670 g. Slight adhesions of aortic cusps	Nothing of note
9	74 F	All branches on both sides filled with firm antemortem thrombus extending to bifurcation	400 g. Marked dilatation of right side	Small chronic duodenal ulcer. Early gangrene of nose. Cystitis

addition and propagation of thrombus on the one hand or autochthonous thrombosis on the other is the important ætiological factor. When the characteristic features of pulmonary emboli are obscured by superadded thrombus their identification is rendered difficult or impossible (Belt, 1939) and a decision has to be made from the associated pathological findings such as the condition of the lungs and pulmonary vessels, evidence of a source of a embolus and the clinical course of the patient. There is little doubt that single or repeated pulmonary emboli may become organized, and with the subsequent addition of thrombus and the development of obstruction of the pulmonary circulation produce a clinical picture of chronic or subacute cor pulmonale (Ljungdahl, 1928; Means and Mallory, 1931; Belt, 1939; Hampton and Castleman, 1940; Carrol, 1950; and Hanelin and Eyler, 1951). Keating *et al.* (1953), however, while conceding the importance of antecedent embolism, could recognize the sequence of embolism followed by thrombosis in only one of their seven cases; they therefore stressed the importance of thrombosis *in situ*. The occurrence of autochthonous thrombosis has been well documented (Billings, 1921; Brenner, 1935; Savacool and Charr, 1941; and Bryson, 1949). The factors that are considered to predispose to thrombosis *in situ* are diffuse pulmonary disease such as tuberculosis, pneumokoniosis, or emphysema, diffuse pulmonary vascular disease, cardiac failure and pulmonary hypertension, dehydration, anoxæmia, and altered coagulability of the blood. The presence of one or more of these factors does not

preclude the occurrence of pulmonary embolism but actually prediposes towards it by encouraging leg vein thrombosis and also predisposes to the spread of secondary thrombus upon a embolus. Apart from the widespread uniform thrombosis which is exemplified in Case 9 and seems undoubtedly to be autochthonous in origin, we are frequently left with a consideration of the history and an examination of the peripheral veins as the only basis on which to determine the origin of the thrombus.

In the present series there was good clinical evidence of embolism and lower limb phlebothrombosis in Cases 1 and 2, while Case 3 had an episode highly suggestive of embolism some six years before death. Case 4 had no episode suggesting embolism and the peripheral veins were free of thrombus. In Cases 5–8 an adequate past history was not available and the occurrence of pulmonary embolism could not be excluded. Thrombus was found in the leg veins in Cases 5 and 7.

Summary and Conclusions

Massive thrombotic occlusion of the main pulmonary arteries is a rare condition occurring perhaps once in five thousand post-mortem examinations. As a syndrome of clinical significance it is probably even rarer. Occasionally it is responsible for a picture of chronic cor pulmonale and the occurrence of unusual murmurs and thrills may suggest the diagnosis of congenital heart disease. The condition should be considered in the differential diagnosis of pulmonary vascular obstruction and a prior history suggesting pulmonary embolism or infarction should lend support for the diagnosis. There appear to be no specific clinical features enabling the diagnosis to be made with confidence and the more acute cases may resemble massive pulmonary embolism. The radiological features are important in the diagnosis but may be difficult to interpret in the presence of underlying cardio-pulmonary disease. Four chronic and five subacute cases have been described and previous papers have been briefly reviewed. The importance of pulmonary embolism in initiating the thrombosis is stressed but a proportion of the cases are apparently the result of thrombosis *in situ*. It was not possible to determine whether pulmonary embolism had occurred in the past other than by inference based on a careful and full case history. Pathological examination of the present cases showed that old thrombus was attached to the main pulmonary artery or straddled the bifurcation and the addition of fresh thrombus had obliterated the pulmonary circulation and led to death.

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THE INTRACARDIAC ELECTROGRAM AS AN AID IN CARDIAC CATHETERIZATION

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Electrocardiograms have been recorded by unipolar leads from the great veins and cavities of the right heart during cardiac catheterization in 30 of 130 cases of congenital and rheumatic heart disease. These intracardiac electrograms have given information that has proved useful in diagnosis. Further, continuous monitoring on an oscilloscope of these tracings, rather than of records from surface leads, adds to the safety of the procedure. In this paper an attempt is made to assess the help thus afforded by intracardiac electrography.

Summary of Relevant Knowledge of Intracardiac Electrograms

Studies of intracardiac electrograms obtained by cardiac catheterization were first reported by Lenègre and Maurice (1945). The normal intracardiac electrogram has been further described by Hecht (1946), Battro and Bidoggia (1947), Sodi-Pallares *et al.* (1947), Levine *et al.* (1949 *a* and *b*) and Kossmann *et al.* (1950) and others. Relevant present knowledge, based on their work, may conveniently be summarized under three headings.

The Normal Intracardiac Electrogram. The intracardiac electrogram consists of the auriculogram and ventriculogram (Fig. 1). The auriculogram is inscribed during atrial depolarization and corresponds to P in surface leads; the ventriculogram is the result of ventricular depolarization and repolarization and corresponds to QRS and T in surface leads.

The shape of the auriculogram bears a fairly constant relation to the position of the electrode. Fig. 2 indicates the form it takes in various chambers and great vessels of the right heart. The complex is wholly upward in the lower part, wholly downward in the upper part and diphasic in the middle part of the right atrium. The form of the ventriculogram varies much more from individual to individual and in different parts of the same heart; even in the same chamber it does not bear nearly so constant a relation to the position of the electrode as the auriculogram. Fig. 3 shows some of the common forms that are recorded from the right side of the heart.

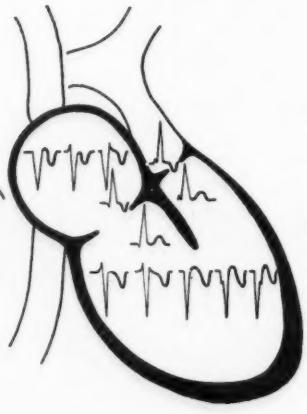
The Electrogram from the Coronary Sinus. The coronary sinus is in close anatomical relation to the left atrium, and to the cavity and epicardium of the left ventricle. Fig 4 demonstrates how these relations affect the form of the electrogram from the coronary sinus. The left atrium is depolarized later than the right atrium: so the intrinsic deflection of the right atrial auriculogram occurs in the early part of the P in a simultaneously-recorded surface lead, while that from the left atrium occurs later, in the second half of P. Therefore the characteristic electrogram from the coronary sinus has an auriculogram of left-atrial type, while the ventriculogram borrows the Q from the cavity of the left auricle and reflects the late R and sometimes the upright T of the left ventricular epicardial surface (Levine and Goodale, 1950).

Endocardial Injury Effects. Pressure of the electrode against the endocardium produces an injury current, giving S–T elevation in the ventriculogram or Sa–Ta elevation in the auriculogram. The injury current may even produce a monophasic deflection of considerable amplitude. Hellerstein and Katz (1948) studied in dogs the effects on the electrogram of endocardial pressure sufficient to produce S–T elevation. Following pressure for five seconds a normal complex appeared after a single beat; but if the pressure lasted four minutes,

FIG. 1.—The intracardiac electrogram. The auriculogram (A) is caused by atrial depolarization, the ventriculogram (V) by ventricular depolarization and repolarization.

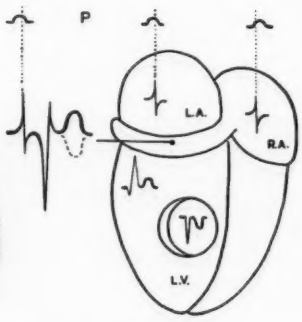
ACCESSION AURICULOGRAM

FIG. 2.—Schema, showing typical auriculogram complexes as they occur in right atrium and ventricle, venæ cavæ, and pulmonary artery. Arrow shows position of sinus node.



VENTRICULOGRAM

FIG. 3.—Schema of right side of heart, showing various forms commonly adopted by the ventriculogram. Ventriculograms with a high, late R are sometimes found on either side of the tricuspid and pulmonary valves.



CORONARY SINUS

FIG. 4.—Schema of posterior aspect of heart, showing anatomical relation of coronary sinus to left atrium and to epicardium and cavity (through "window") of left ventricle. The intrinsic deflection of the auriculogram from the right atrium occurs early in P in a simultaneous surface lead; that from the left atrium occurs late in P.

S–T did not return to normal for over 20 minutes. This S–T elevation, although conspicuous in the intracardiac electrogram, is not seen in simultaneously-recorded præcordial leads (Levine *et al.*, 1949 *b*) or even in direct leads from the epicardium (Borchardt *et al.*, 1948).

Intracardiac electrography has been used to investigate various fundamental electrocardiographic problems, but the only direct clinical applications that have hitherto been suggested are its use in analysing complex arrhythmias (Ferrer *et al.*, 1949; Steinberg *et al.*, 1952) and as a help in positioning the catheter tip at different points within the coronary venous system (Goodale *et al.*, 1949).

Method

The exploring electrode consists of an inlaid band of nickel-silver a few millimetres from the tip of a single-lumen Cournand cardiac catheter. This is connected to a terminal at the proximal end by a wire in the wall of the catheter, so that the lumen remains wholly patent. Catheters of this type are used in sizes 5 to 9, French gauge (United States Catheter and Instrument Corp.). The proximal terminal is connected by a unipolar system of Wilson type, to one channel of a three-channel Triplex electrocardiograph (Elmqvist). The other two unipolar leads are placed on the surface of the body, usually at positions VR and V1. Simultaneous permanent recordings are made from unipolar surface and intracavity leads by an optical system on photosensitive paper, and the intracardiac electrogram is also observed continuously on a Cossor double-beam oscilloscope. By means of a capacitance electromanometer (Southern Instruments, Limited) simultaneous pressure-pulse tracings can be recorded on the fourth channel of the Triplex machine and monitored on the second channel of the oscilloscope.

Personal Observations

Location of the Catheter Tip. Location of the catheter tip within the heart is possible from observation of the intracardiac electrogram. For example, in Fig. 5, the catheter tip lies in the right atrium. Its movement from a low to a high position in the atrium is recorded by the electrogram, the auriculogram being at first upright, then diphasic, then wholly downward. The tracing in Fig. 6 was recorded as the catheter tip was being withdrawn from the pulmonary artery to the right

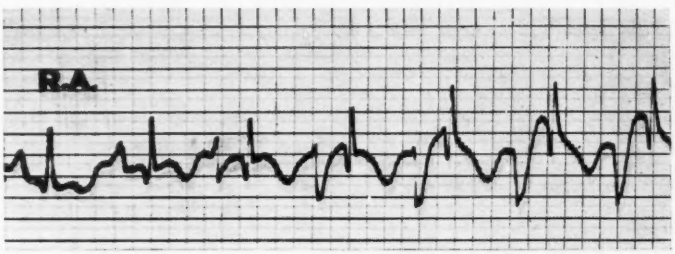


Fig. 5.—Catheter in right atrium. Wholly upright auriculogram in first two electrograms denotes electrode position low in atrium; diphasic auriculogram in third complex denotes mid-atrial position; subsequent downward auriculograms denote electrode high in atrium.

Fig. 6.—Catheter withdrawn from pulmonary artery to right ventricle. Intracardiac electrogram (above) and undamped pressure tracing (below) show change of electrode position. First three ventriculograms from infundibulum show rsR′ pattern; last ventriculogram (rS) is commonest pattern from right ventricular cavity.

ventricle. The change in position is shown not only by the altered pressure pulse, but also by characteristic alterations in the ventriculogram. In Fig. 7 the fact that the intrinsic deflection of the auriculogram occurs in the second half of the P in a simultaneous surface-lead electrocardiogram suggests that the arterialized blood withdrawn at this point was from the left atrium or nearby pulmonary vein. The left-ventricular cavity pattern of the ventriculogram, with Q as the sole initial deflection, confirms that the sample was, in fact, from the left atrium.

When the catheter tip lies in the coronary sinus the characteristic pattern of the coronary sinus electrogram, as described above, is seen (Fig. 8). The late intrinsic deflection of the auriculogram cannot always be identified with certainty on the oscilloscope, but the ventriculogram may be diagnostic.

Fig. 9 shows a tracing made during the cardiac catheterization of a cyanosed patient thought to have a pseudotruncus arteriosus. The catheter passed from the right atrium into a high-pressure chamber which might have been a single ventricle. The ventriculogram, however, showed an R preceding S, as in the normal right-ventricular ventriculogram. This R, due to depolarization of the inter-ventricular septum from left to right, argued that a septum was present. This was later proved by angiocardiography.

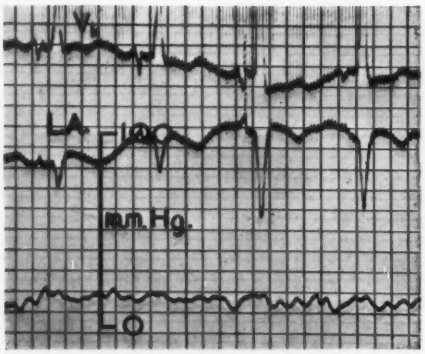


FIG. 7.—Catheter tip in left atrium (entered through atrial septal defect). Above downwards: electrocardiogram lead V1, intracardiac electrogram, pressure. The intrinsic deflection of the auriculogram occurs late in P in lead V1. The ventriculogram is of left-ventricular-cavity pattern (Q).

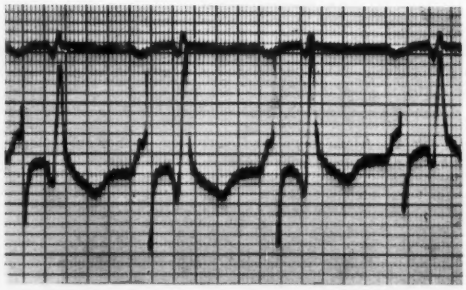


FIG. 8.—Catheter tip in coronary sinus. Electrocardiogram, lead VR above, intracardiac electrogram below. The intrinsic deflection of the auriculogram occurs late in the P in lead VR. The ventriculogram reflects the Q of the left ventricular cavity and the high late R of the left ventricular-epicardial surface.

Indication of Injury. Fig. 10 shows a tracing recorded while the catheter tip was in contact with the right ventricular endocardium. The injury current thus produced caused progressive elevation of S–T in the ventriculogram, until, after a right ventricular ectopic beat, a normal ventriculogram recurred; possibly the ectopic beat dislodged the catheter tip from the endocardium. Such S–T elevations as these may be 5 mV. or more in amplitude. We have recorded similar elevations of the Sa–Ta segment of the auriculogram, arising from pressure of the catheter against the atrial endocardium.

DISCUSSION

In order to reduce the risk attached to cardiac catheterization it is usual for one member of the team to watch the electrocardiogram throughout the procedure. There are certain advantages in watching the intracardiac electrogram rather than surface-lead tracings.

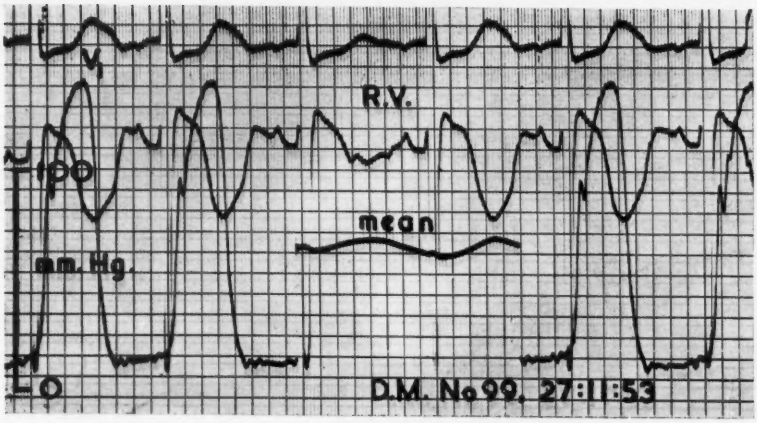


FIG. 9.—Tracings from chamber wrongly postulated as single ventricle. Above downwards: electrocardiogram, lead V1, intracardiac electrogram, pressure. R in intracardiac electrogram means presence of interventricular septum.

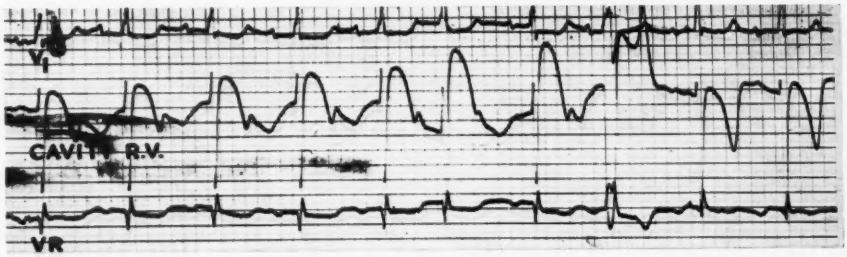


FIG. 10.—Catheter tip pressing against right ventricular endocardium. Injury current causes progressive elevation of S–T in intracardiac electrogram but not in lead V1 or VR. After right ventricular ectopic beat normal ventriculograms recur.

From the point of view of both patient and operator it is important to reduce the screening time to a minimum. It is therefore helpful, particularly during withdrawal, to be able to locate the catheter tip by watching the intracardiac electrogram.

Although deliberate catheterization of the coronary sinus may be a relatively safe procedure, accidental entry occurs in some 16 per cent of cardiac catheterizations (Culbertson *et al.*, 1949) and may not be recognized: in these circumstances it is dangerous. McMichael and Mounsey (1951) reported five cases of præcordial distress and collapse from accidental catheterization of the coronary sinus; in one patient the coronary sinus was perforated. They stressed the difficulty of recognizing by screening in the supine position that the catheter was in the coronary sinus and not in the right ventricle, and they suggested turning the patient into the left anterior oblique position. This, however, is inconvenient, as the catheter is usually in the left arm. Moreover, Goodwin (1953) has suggested that movement of the patient with the catheter in the heart is dangerous. Goodale and Levine (1949), having deliberately catheterized the coronary sinus by screening in two planes, used the intracardiac electrogram to locate the catheter tip more precisely within the coronary venous system. The present study has shown that routine monitoring of the intracardiac electrogram readily

shows that the catheter tip has entered the coronary sinus, and that it thus helps to prevent dangers that attend unrecognized coronary sinus catheterization.

Although endocardial trauma seems to occur much less frequently in man than in experimental animals, Goodwin (1953) reported a case in which damage to the right ventricular endocardium during an apparently uneventful catheterization led to the patient's death. As a precaution against this kind of accident the oscilloscope should be watched throughout the catheterization for the appearance of changes in the electrogram due to injury currents. The S–T elevation in the ventriculogram is readily recognized in the oscilloscopic tracing, and easily differentiated from, say, ectopic beats. Its appearance is regarded as an imperative indication for withdrawal of the catheter, since, although it appears with the slightest pressure of the electrode, it represents possible endocardial damage. This is particularly important during blood sampling when the catheter tip may lie within the right ventricle for a minute or more.

In addition to the help thus given at the time of catheterization intracardiac electrography can also assist the later analysis of tracings. The shape of the electrogram will often permanently identify the site of a pressure pulse or a blood sample. Injury currents provide a means of recognizing that unexpectedly low pressure pulses are the result of partial occlusion of the catheter by endocardium, and are consequently invalid.

The technique of intracardiac electrography described here is a simple addition to routine cardiac catheterization; it is neither expensive nor time-consuming. This preliminary report is based on a modest series of cases investigated by its aid, but it is felt that the help which it gives warrants its consideration for further and wider trial.

Summary

Studies of the human intracardiac electrogram have been made during cardiac catheterization.

The normal electrogram in the right atrium and ventricle and in the coronary sinus is described, together with the effects of endocardial pressure by the catheter.

The use of intracardiac electrograms rather than surface-lead electrocardiograms lessens the risk of cardiac catheterization by reducing screening time, and helps to prevent both trauma to the endocardium and accidental catheterization of the coronary sinus. It helps the later interpretation of pressure tracings by graphically locating their site of origin and by indicating the cause of certain common distortions.

The technique described is simple, and neither expensive nor time-consuming. It deserves a wider trial.

I am very grateful to Professor I. G. W. Hill for clinical and laboratory facilities, and for his help in the preparation of the manuscript, and I acknowledge the assistance and facilities given by the technical and secretarial staff of the Department of Medicine, the nursing staff of the Professorial Unit and the staff of the Radiological Department, Dundee Royal Infirmary.

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THE ATRIAL PRESSURE TRACING IN CONGENITAL HEART DISEASE

BY

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A case of pulmonary stenosis showing terminally the signs of an associated tricuspid incompetence prompted an enquiry into the frequency of tricuspid incompetence in congenital heart disease. From the theoretical standpoint, two distinct types of incompetence—structural and functional—may be recognized. It is well known that structural incompetence may be associated with organic abnormalities of the valve region, particularly in Ebstein's disease. However, functional incompetence is generally held to be rare in congenital heart cases, although instances of pulmonary stenosis showing this complication have been described (Biörck *et al.*, 1952; and Campbell, 1954). Against this view must be set the fact that the clinical detection of tricuspid regurgitation is difficult unless the condition is advanced, and lesser degrees of regurgitation may thus have escaped notice.

The development of electro-manometric technique has allowed a detailed examination of human atrial pressure curves, and some knowledge of their form in the presence of tricuspid regurgitation has been obtained by a study of cases with rheumatic heart disease (Bloomfield *et al.*, 1946; Müller and Shillingford, 1954; and Korner and Shillingford, 1954). It was therefore thought of interest to review tracings from a large group of pulmonary stenosis cases with particular reference to possible evidence of tricuspid regurgitation. Tracings from three cases of Ebstein's disease have also been examined, and the diagnostic value of an abnormal atrial pressure curve is discussed.

Normal Atrial Pressure Curves

The pattern of the normal atrial pressure curve varies considerably according to the degree of damping that is introduced into the system, but with optimal damping and natural frequency the curve assumes the form illustrated in Fig. 1. This curve was first described for the experimental animal (Wiggers, 1923), but Fowler *et al.* (1953) have now confirmed that the human tracing has a similar form, and from a large group of observations on normal subjects quote the following average pressures for the various waves. The pressures are given in mm. Hg from a line 10 cm. anterior to the spine.

a wave 5·5 mm.	*x* descent 3·0 mm.
c wave 3·5 mm.	*x'* descent 1·5 mm.
v wave 4·5 mm.	*y* descent 2·5 mm.

The recording system used in this laboratory (Southern Instruments electro-manometer with Kelvin-Hughes direct writing recorder) had a satisfactory natural frequency (>15 c.p.s. with No. 8 Cournand cardiac catheter attached). The degree of damping was normally not sufficient to obliterate any of the atrial waves, although in some patients with a large *a* wave, the *c* wave did tend to merge into the descending limb of the *a* wave.

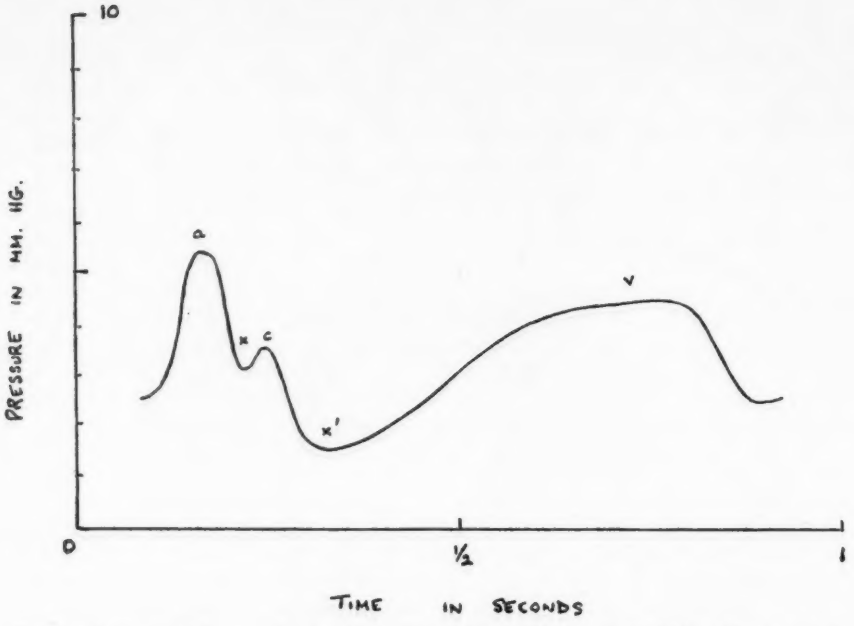

FIG. 1.—Average atrial pressure curve in normal subjects. The average heights of the *a*, *c*, and *v* waves and the average depth of the *x*, *x'*, and *y* descents are given in the text.

ATRIAL TRACINGS IN PULMONARY STENOSIS

Fifty-one tracings from 40 different cases have been examined. Generally the outstanding feature is a large *a* wave (Fig. 2). The atrial systolic reading is increased in many forms of congenital heart disease (Shephard, 1954), but this is particularly true of pulmonary stenosis, the average value in the present series being 10 mm. Hg. In 18 cases it was not possible to detect a distinct *c* wave; it was present in the remaining 22, although usually represented only by a small hump of 1 mm. or less on the descending slope of the *a* wave. The *x'* descent was well marked and clear cut in most tracings, the average value (2·3 mm. Hg) being close to normal. Extreme values were 10 and −2 mm. Hg, but most lay in the range 0–5 mm. Hg. The *v* wave was again of normal amplitude in most instances, the average for the group being 4·5 mm. Hg. The decline of the *v* wave was perhaps a little less marked than in the normal person, the average pressure at the *y* descent being 3·7 mm. Hg.

In 10 of the 40 cases, the rising phase of the *v* wave showed an additional pressure fluctuation. Often small, this in a few instances overshadowed the true *v* wave (Fig. 2). This corresponds in timing with the *s* wave, described as a feature of tricuspid incompetence by Bloomfield *et al.* (1946), and it seems possible that this additional wave indicates some degree of functional regurgitation at the tricuspid valve. Korner and Shillingford (1954) have described obliteration of the *x'* descent as a further feature of tricuspid leak in rheumatic patients, but it is unlikely that these findings are applicable to pulmonary stenosis. In a normal heart the *x'* descent is probably initiated by two factors—descent of the base of the heart, and active relaxation of the atrium. In rheumatic heart disease, the atrium is diseased and often fibrillating, so that while the first factor may operate, active relaxation is not possible. On the other hand, in pulmonary stenosis the atrium is large

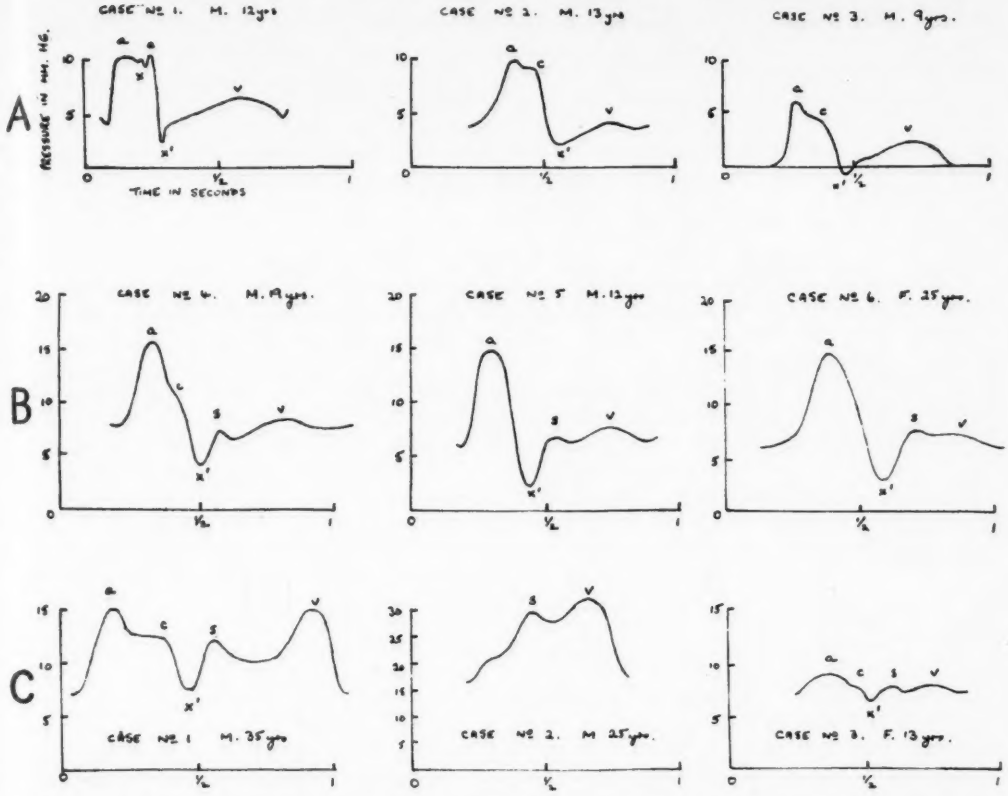
A
B
C
PRESSURE IN MM. HG.
TIME IN SECONDS
CASE Nº 1. M. 12 yrs
CASE Nº 2. M. 13 yrs
CASE Nº 3. M. 9 yrs.
CASE Nº 4. M. 9 yrs.
CASE Nº 5 M. 12 yrs
CASE Nº 6. F. 25 yrs.
CASE Nº 1 M. 35 yrs
CASE Nº 2. M 25 yrs.
CASE Nº 3. F. 13 yrs.

FIG. 2.—Atrial pressure curves where the pressure on the right side of the heart is raised. (A) From 3 typical cases of simple pulmonary stenosis with the *c* wave almost hidden in the *a* wave. (B) From 3 severe cases of pulmonary stenosis where the average right ventricular systolic pressure was 153 mm. Hg, showing an *s* wave: this was thought to indicate some degree of tricuspid regurgitation. (C) From 3 cases of Ebsteins disease, showing *s* waves also (see text).

and muscular, and the *x'* descent is potentially greater than normal; obliteration of the *x* descent would not therefore be expected except as a late sign of tricuspid leak.

It might be anticipated that tricuspid regurgitation would develop particularly in those cases where the right ventricular pressure was high, or the valve region had been subjected to strain for a long period. It therefore seems significant that the 10 cases showing an *s* wave were all particularly severe, the average right ventricular systolic pressure being 153 mm. Hg, as compared with 112 mm. Hg for the remainder of the group. Further, most of these 10 were adults, the average age for the group being 21 years, and a number showed severe electrocardiographic evidence of myocardial strain. However, clinical evidence of tricuspid regurgitation was not noted in any of these patients. The one case showing clinical signs of this complication was even older (37 years); he died of ventricular fibrillation a few days after an operation that had been successful in relieving his stenosis.

ATRIAL TRACINGS IN EBSTEIN'S DISEASE

The electro-manometer records of three cases are available for analysis. These provide by way of comparison the pressure tracings associated with a congenital structural abnormality of the

tricuspid valve region. The pattern and average level of pressure in the atrium varies considerably, probably owing to differences in the amount of muscle incorporated into the effective atrial chamber, but the mean atrial pressure is high in all three patients. Disturbances of electrical conduction are shown by a delayed *c* wave in Cases 1 and 3, and auricular fibrillation in Case 2. The main feature that is common to the three tracings seems an *s* wave. This is similar to the *s* wave seen in a number of the pulmonary stenosis cases, but is more marked, as might be expected from the higher mean atrial pressure and the more obvious clinical manifestations of tricuspid incompetence.

Discussion

Clinical cases of tricuspid incompetence are rare in congenital heart disease, being confined to organic abnormalities of the tricuspid region and long standing cases of simple pulmonary stenosis. However, study of a large group of pressure tracings from the right atrium suggests that a smaller degree of tricuspid leak may be more common, particularly in older cases of pulmonary stenosis. The basic features of the regurgitant tracing seem to differ slightly from those observed in mitral stenosis, probably owing to the more healthy condition of the right atrium, and a large *x'* descent may precede the *s* wave. Many cases of pulmonary stenosis withstand a high right ventricular pressure without developing any evidence of regurgitation, and this can again be attributed to the healthy condition of the myocardium and atrio-ventricular ring during youth. At cardiac catheterization it is common to find a greatly enlarged right atrium, while the tricuspid orifice is still apparently of normal size. However, it is not surprising to find that as adult life is reached, the more severe cases develop some dilatation in the region of the tricuspid valve leading to functional incompetence. It is well recognized that functional incompetence is a reversible condition provided that severe liver damage has not occurred; however, in the absence of treatment, it is liable to progress towards a fatal conclusion. The fact that some cases of pulmonary stenosis may show electromanometric signs of tricuspid incompetence before reaching the age of 21 is a further pointer to the importance of early treatment in this condition.

The main diagnostic features of catheterization in Ebstein's disease have previously been considered the coiling of the catheter in the massive right atrium, and a left-to-right shunt through an atrial septal defect (Baker *et al.*, 1950). Catheterization is not to be undertaken lightly in Ebstein's disease owing to certain special risks (Engle *et al.*, 1950), but if it does prove necessary the present study suggests that certain features of the pressure tracing, particularly a high mean atrial pressure and a regurgitant *s* wave may help in reaching the diagnosis.

Summary

Atrial pressure tracings have been examined in 40 cases of pulmonary stenosis. The main feature in all was a large *a* wave, but ten older cases with a high right ventricular pressure showed also an abnormal *s* wave, suggesting the development of some functional tricuspid incompetence. In three cases of Ebstein's disease, the mean atrial pressure was high, and an *s* wave confirmed the presence of tricuspid incompetence.

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THE RESULTS OF VALVOTOMY FOR SIMPLE PULMONARY STENOSIS

BY

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The medical aspects of simple pulmonary stenosis, i.e. valvular stenosis with a closed ventricular septum, have been discussed recently (Campbell, 1954). We wish now to describe the results after pulmonary valvotomy, as we have those after anastomotic and direct operation in Fallot's tetralogy (Campbell and Deuchar, 1953: Campbell, Deuchar, and Brock, 1954). We have carried out the follow-up in the same way, but some important differences need emphasis.

In Fallot's tetralogy the disability of the patient is always the reason for operation, and improvement is judged mainly by the increased capacity and lessened cyanosis. A smaller heart or less right ventricular preponderance can not be expected, since the right ventricle is still working against a pressure that is the same, or nearly the same, as the systemic pressure. In fact, if the result is good clinically, success is judged by an absence of too much increase in the size of the heart or of right ventricular strain in the electrocardiogram, for after four or five years some patients are showing this latter change. Fortunately, so far, this is not reflected in any loss of ground clinically, but taking a longer view, it probably will be and this means that the great improvement obtained after these operations may generally be limited to perhaps ten or twenty years.

In simple pulmonary stenosis there are several differences. Many patients have enough disability to make this the main reason for operation, and the result can be judged in the same way by the improvement in their capacity and cyanosis, if this was present. Others, however, have little disability and operation is advised because of the high pressure in the right ventricle and the cardiographic signs of increasing right ventricular strain. We have, therefore, assessed the improvement of some patients by their increased capacity as well as by objective methods and of others only by the latter because they could do so much before; though many who said they had little disability before operation found, in fact, that they could do more and do it more easily afterwards.

Because of this the results are sometimes less dramatic to these patients than to those with Fallot's tetralogy, but from the longer point of view the operation is a better one as it comes nearer to the ideal of making the heart normal. After a successful operation, there is often the satisfaction of seeing a large heart become smaller (Fig. 1) and no reason to expect that it will ever become larger: generally there is a diminution or even a disappearance of right ventricular strain (Fig. 2) instead of an increase as there may be after operation in Fallot's tetralogy. If the valve does not narrow again from fibrosis or other changes, the improvement should last indefinitely. Some patients have, however, reached such a late stage with a large heart and gross right ventricular strain that operation can hardly be expected to restore them to normal, though it should improve them.

Further, cardiac catheterization plays a more important part in the assessment of the results, because the pressure in the right ventricle is often a main reason for the operation. We think, however, on the evidence to be presented that improvement in the electrocardiogram makes it certain that the right ventricular pressure has been reduced, even without catheterization.

Four years ago we reported the results after valvotomy in 17 cases of simple pulmonary stenosis

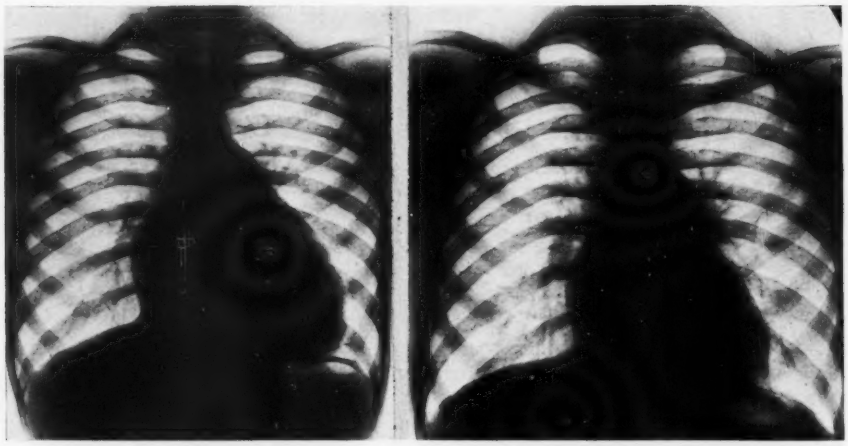

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FIG. 1.—Great reduction in heart size after valvotomy for simple pulmonary stenosis with cyanosis. (A) Before operation, c.t.r., 59 per cent (m.t.d 14·5/24·5 cm.). (B) Four years after, c.t.r. 49 per cent (m.t.d. 14·0/28·5 cm.). Case V41 (O546).

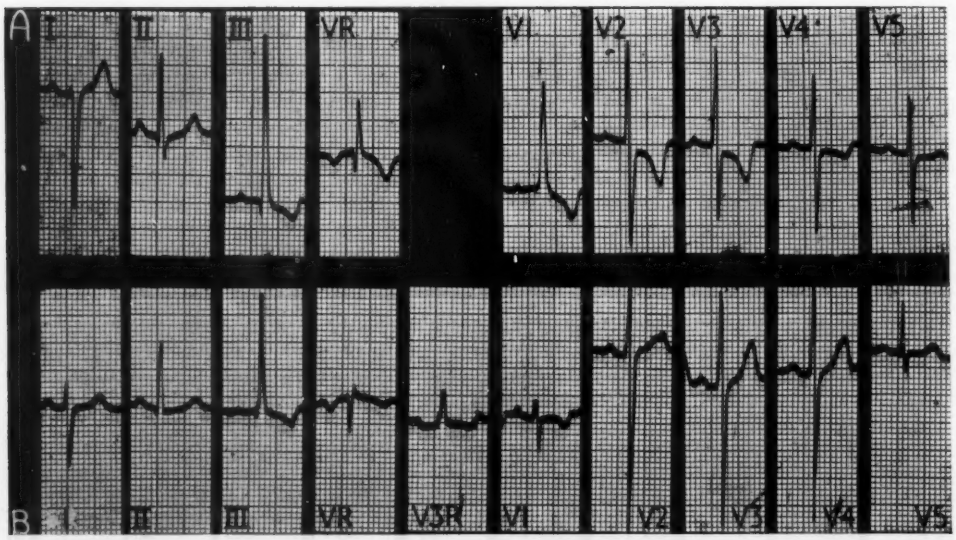

FIG. 2.—Disappearance of right ventricular strain and even of preponderance after valvotomy for simple pulmonary stenosis with cyanosis. (A) Before operation, showing T inversion to V4. (B) Three years after, showing T inverted in III and V1 only, and much less right ventricular preponderance. Case V47 (P208).

and showed that the right ventricular pressure could be reduced to half of its previous level (Case 30, Brock and Campbell, 1950). Now the number who have been submitted to operation has risen to 92, but this detailed follow-up is concerned with the 58 patients who have been operated on at Guy's Hospital: similar results have been obtained in the other 34 patients. We have divided them according to the presence or absence of central cyanosis when they were out-patients, and 25 were cyanotic and 33 were acyanotic.

Most of those who were acyanotic had an arterial oxygen saturation of 95 per cent or above, but it was between 92 and 94 per cent in four, in whom we thought there was no central cyanosis at rest. In three of these and in four others—nearly one-quarter of the whole—there were good reasons for thinking that they sometimes had a right-to-left shunt with exercise, and several others complained of some degree of peripheral cyanosis especially when it was cold.

The degree of arterial anoxæmia was very variable in those who had central cyanosis at rest. In seven it was under 70 per cent, in four under 80 per cent, and in three under 85 per cent. This means that more than half were below this level but nearly half had only a small shunt with an arterial oxygen saturation above this. In six it was between 85 and 89 per cent, two of these looking more cyanotic than this would suggest; in two it was 90 per cent, in two it was 91 per cent, and the cyanosis which seemed much more severe must have been mainly peripheral; and in the last, who became much more cyanosed during her paroxysms of tachycardia, it was 92 per cent.

Sex and Age Incidence

Simple pulmonary stenosis has no special predeliction for either sex. This was also true of the 58 patients who had operations (27 male, 31 female) though, probably by chance, there were rather more women among the cyanotic cases.

The patients were older than those with Fallot's tetralogy and one-third were over 20 years of age (Table I). Most were between 5 and 29 years, but three cyanotic children needed operation when they were only 4 years old, and five patients were over 30, the eldest being 42 years.

TABLE I

Sex and Age Incidence of Patients having Valvotomy for Simple Pulmonary Stenosis

Age in years	0–4	5–9	10–14	15–19	20–24	25–29	30–39	40 and over	Total
Acyanotic	0	5	10	7	4	4	2	1	33
Cyanotic	3	6	3	4	3	4	2	0	25
Male	2	4	8	6	4	1	2	0	27
Female	1	7	5	5	3	7	2	1	31
Total	3	11	13	11	7	8	4	1	58

At first sight it is surprising that the age incidence of these patients who have had an operation is much the same as that of all those we have seen. If our selection of patients for operation is reasonable this means that there is no special age at which symptoms or other indications, such as the right ventricular pressure, become progressively important, and that this may happen at any time though not very often after 24 in men or after 29 in women.

The sex did not appear to influence the age incidence greatly except that ten of the thirteen patients over 25 were women.

Operative Mortality

Pulmonary valvotomy for simple pulmonary stenosis is not a dangerous operation if the patient is not left till too late. The first acyanotic patient, a girl, aged 9, who had congestive failure and a

huge heart died during the operation, but 32 acyanotic patients have been operated on since without a death.

The early cyanotic patients had reached an advanced stage of their disease and four of the first five died, but since then there have been only three deaths among twenty cases. Two of these three were gravely ill; one was a man, aged 33, who had got on well until some years before, but had auricular fibrillation, a very large heart, and congestive failure with recurrent ascites, so that he had been almost bedridden for the last year. The second was a girl, aged 19, who had obtained no lasting benefit from a subclavian-pulmonary anastomosis in America some years before, and had developed deep cyanosis and congestive failure. The third, a girl, aged 25, had increasingly frequent paroxysms of ventricular tachycardia which proved impossible to control after her operation. Thus, since the end of 1949, excluding the two with heart failure, only one patient has died, and if we had allowed more time to bring her paroxysms under better control before operation, the fatal result might have been avoided.

The total operative mortality was 14 per cent, but 5 of the deaths were in the first 6 operations and since then it has been less than 6 per cent: even these later cases included many who were gravely disabled and nearly all had a right ventricular systolic pressure over 100 mm. Hg, often with severe signs of right ventricular strain.

The Results after Pulmonary Valvotomy

The results had been good in 46 of the 50 patients who survived operation. Among the 33 acyanotic patients only one has died, leaving 32 to be followed. Among the 25 cyanotic patients, seven have died, leaving 18 to be followed. Of the 50 survivors, 11 have been followed for from four to six years, 10 for three years, 13 for two years, 13 for one year, and 3 for some months only. None has been lost sight of, but we have accepted reports from their doctors for two patients overseas whom it has not been possible to examine. All the others have been seen regularly. The results are shown in Table II. Several individual cases were reported in detail in our earlier paper so this has not been thought necessary here, but the subsequent history of Case 7 is given shortly.

TABLE II

Results of Valvotomy in Simple Pulmonary Stenosis

	No. of cases	Deaths	Good results	Poor results
P.V.S. pure (acyanotic)	33	1 *	28 ‡	4 ‡
P.V.S. with P.F.O. (cyanotic)	25	7 †	18 ‡	0

* First patient.
† Four of first 5 patients.
‡ One case in each of these groups had pulmonary regurgitation.

A woman, aged 26, was deeply cyanosed and could walk no more than 100 yards; she was losing ground rapidly. Eleven months after operation she was leading a normal life and gave birth to a child with no special difficulty. After six years she is leading an active life as a housewife and can walk several miles and do all the work she wants.

Cyanotic Group. Here it is easy to judge the results because all the patients were greatly improved in their capacity and in their colour and all but one had symptoms that by themselves were severe enough to indicate operation.

This clinical improvement was confirmed by the heart becoming smaller in 10 patients (Fig. 1 and 3) including all but one of those where it was much enlarged. In 11 of the 12 with evidence of right ventricular strain before operation, this became less and in 5 the change was specially striking (Fig. 2 and 6). The right ventricular pressure was greatly reduced in all the nine who have had

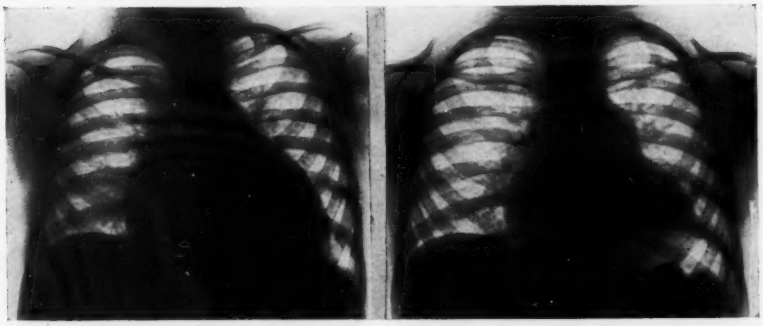

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FIG. 3.—Great reduction in heart size after pulmonary valvotomy in a child who developed severe symptoms and cyanosis early. (A) Before operation, c.t.r. 68 per cent (m.t.d. 11·3/16·8 cm.). (B) One year after, c.t.r. 59 per cent (m.t.d. 10·1/17·1 cm.). Case V94 (O897).

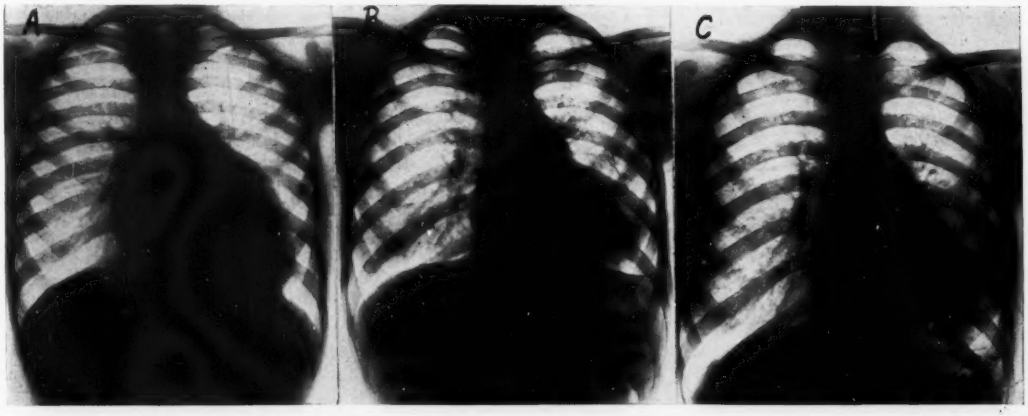

FIG. 4.—Great reduction in heart size after valvotomy for acyanotic pulmonary stenosis. (A) Before operation, showing great enlargement (c.t.r. 63%: m.t.d. 12·6/19·8 cm.) and the characteristic humped left border due to hypertrophy of the right ventricle. (B) Much diminution in size eighteen months after operation (c.t.r. 54%: m.t.d. 11·8/22 cm.). The pulmonary arteries seem larger and the pulmonary blood flow more normal. (C) Three years after operation she had grown a lot and indulged in an active life, but the increase in the chest is greater than in the heart (c.t.r. 53%: m.t.d. 12·2/23 cm.). Case V39 (O468).

catheterization after operation, nearly always to less than half of what it had been before and on an average from 127 to 44 mm. (Table VII).

Acyanotic Group. Here it is sometimes more difficult to judge the improvement on clinical grounds, because many patients had few symptoms and were operated on because of the high right ventricular pressure and right ventricular strain. Sixteen of the 32 patients, however, had severe symptoms and all but one of these were greatly improved: unfortunately one has been unable to take much advantage of this as he has developed pulmonary tuberculosis. The symptoms were much improved in 8 others but they had not been severe enough by themselves to justify operation. There were 5 others where they were so slight that they were little guide to the result: for example,

one man who had been leading a normal life could cycle up a particular hill on the way to work more easily than before, but such a change is not really reliable.

The results were disappointing in four patients only, all of whom were acyanotic. One woman, aged 25, seemed better at first and resumed the work that she had had to give up two years before, but a year later she found it difficult and seemed no better than before, although the pressure had been reduced from 112 to 55 mm. Hg (Case V80). The second, a boy aged 14, had few symptoms before operation in spite of his high right ventricular pressure; he developed bundle branch block during the operation and it has persisted; he cannot do so much as before and the heart is larger (Case V104). The third, a man, aged 33, has not obtained great benefit though the right ventricular pressure has been reduced from 190 to 107 mm. (Case V108). The fourth, a girl, aged 10, was operated on six months ago and does not seem much better and her heart has become larger: there is some pulmonary regurgitation but it hardly seems enough to account for her condition (Case V121).

The clinical improvement was confirmed in 7 patients by a diminution of heart size, which was sometimes very striking (see Fig. 4 and 10), and in most others there was little or no enlargement before operation and no change was expected or found. Further confirmation was obtained by diminution of right ventricular strain in 16 patients (Fig. 7–9), though sometimes this was less than was hoped for judged by the good results in other ways. In all the 15 patients who had been re-catheterized the result has been good and the right ventricular pressure has been reduced, generally to between one-half and one-third of the previous level (Table VIII).

Pulmonary Regurgitation. When pulmonary valvotomy was under consideration, the possible production of pulmonary regurgitation was one of the things that was feared. When we reported the early results we had not seen this happen (Brock and Campbell, 1950), but since then it has occurred in three of these patients and must be remembered as one of the risks to be considered in advising operation.

In one (Case V69) who was able to do more and felt better, the cardiothoracic ratio increased from 53 to 57 but is now back to 55 per cent; even this is disappointing because an increase from 47 to 53 in the two years before operation was one of the main reasons for advising it. The second (Case V75) has also improved and the heart has become rather smaller, so probably the regurgitation is slight. The third (V121), a recent case, has shown a disappointing result and the degree of pulmonary regurgitation hardly seems an adequate reason for this.

Cyanosis and Polycythaemia

Many of the early patients had severe cyanosis and an arterial O_2 saturation between 60 and 80 per cent. The heavy mortality at this stage showed that the operation should have been due earlier and made us think that the onset of cyanosis might be an urgent indication: this is true for progressive or severe cyanosis but is not always so for the slighter degrees of cyanosis.

The cyanosis can be abolished much more easily than with Fallot's tetralogy. When the arterial O_2 saturation was above 70 per cent., it has always become normal and all cyanosis has disappeared. Where it was below this, it has always become much better, rising to a figure above 85 per cent, and generally to normal even in this group (see Table VII).

Cyanotic cases develop polycythæmia and an increased hæmoglobin percentage in the same way as those with Fallot's tetralogy, though the average increase is rather less. With the improvement of the cyanosis after operation the polycythæmia and hæmoglobin percentages return towards normal, even more decisively than in Fallot's tetralogy after a successful operation. In the 17 patients where the results are available one to six years after operation, the hæmoglobin fell from an average of 120 to 88 per cent, and its range before and after pulmonary valvotomy is shown in Table III.

The Size of the Heart after Operation

With Fallot's tetralogy a successful operation, whether anastomotic or direct, tends to be followed by some increase in the size of the heart and the best thing that can be hoped for is that there

TABLE III

THE FALL IN THE HAEMOGLOBIN PERCENTAGE AFTER VALVOTOMY IN SIMPLE PULMONARY STENOSIS

	Hæmoglobin percentage						
	80–89	90–99	100–109	110–119	120–129	130–139	140–159
Before valvotomy	—	4	2	2	4	3	2
After valvotomy	10	5	2	—	—	—	—

is no further increase. With simple pulmonary stenosis, however, the position is quite different and a large heart may be expected to become smaller (Fig. 1, 3, 4, and 10). There are 19 cases where figures are available and the patient has been followed for three years. In the 9 with a larger heart (c.t.r. 54% or over) the decrease was 10 per cent, most but not all of this change being seen in the first year. The average cardiothoracic ratio was 60 and after a year it had fallen to 55·8, and after three years to 53·8 per cent (Table IV). Individual results of all those with a large heart are shown in Table V, where it will be seen that Case V40 was alone in showing no reduction in size, though sometimes, e.g. Case V45, the reduction was less than one hoped for. In the 10 with a smaller heart (c.t.r. 53% or less) the average figure was 47·6 per cent, and three years later it was just the same. Some of these decreased a little but some of the very small hearts became larger with increasing activity (Fig. 5). The cyanotic and acyanotic cases were analysed separately but, in fact, the behaviour of the heart as regards its size was the same in the two groups so they have been combined.

TABLE IV

REDUCTION IN HEART SIZE AFTER VALVOTOMY IN SIMPLE PULMONARY STENOSIS

	Cardiothoracic ratio			
	Before operation	After 1 year	After 2 years	After 3 years
C.t.r. 54% and over (9 cases)	60·0	55·8	54·1	53·8
C.t.r. 53% and less (10 cases)	47·6	48·5	48·1	47·6

In the cyanotic group the heart became much smaller in 7 patients (Fig. 1, 4, and Table V), including all the five where the cardiothoracic ratio was over 60 per cent, and smaller in 3 others and there was only one (V40) where a large heart did not become smaller; there was no obvious reason as the result was very good in other ways. In the acyanotic group it became smaller, sometimes very much so, in 7 patients (Fig. 3 and Table V) and in another 22 there was little or no enlargement before operation and no change was expected or found.

Only three patients were disappointing in this respect. One has been mentioned in the section on pulmonary regurgitation (Case V69). The other two were among the four with poor clinical results and the heart became larger, c.t.r. 51 to 58 per cent after one year in Case V104 and from 59 to 62 per cent after six months in Case V121.

ELECTROCARDIOGRAPHIC CHANGES AFTER OPERATION

The pattern of T inversion spreading across the chest leads to V4 or further is common in severe cases of simple pulmonary stenosis and is one of the strong indications for pulmonary valvotomy. It is, therefore, of interest to see how far this pattern can be reversed after a successful valvotomy,

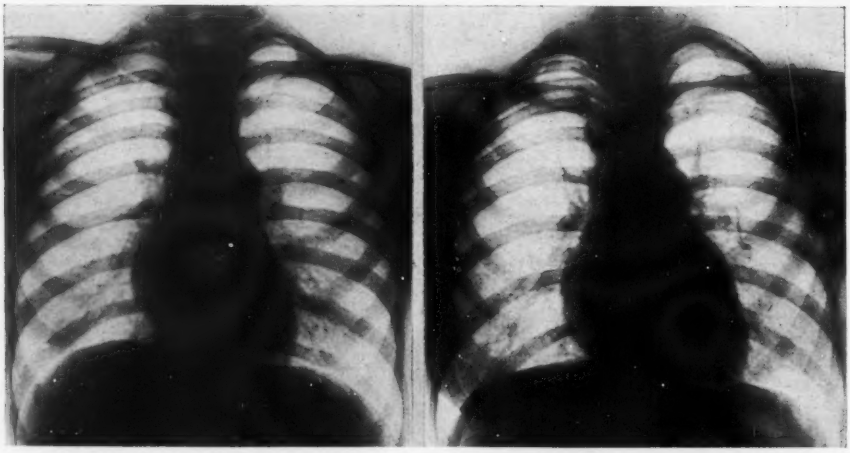

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FIG. 5.—A small heart increasing to normal size with increasing activity after valvotomy. (A) Before operation, c.t.r. 44 per cent (m.t.d. 10·0/22·5 cm.). (B) A year after, when she was leading a very active life, c.t.r. 48 per cent. (m.t.d. 11·9/25 cm.). Case V89 (O715).

TABLE V

REDUCTION OF CARDIOTHORACIC RATIO AFTER VALVOTOMY IN SIMPLE PULMONARY STENOSIS

Case No.	Age and sex	Before operation	After operation			
			1 year	2 years	3 years	4 years
			Acyanotic			
V39	9 F	63	56	54	53	52
V45	29 F	68	63	61	63	62
V46	8 M	56	52	52	53	54
V75	6 F	63	58	58	—	—
V88	11 M	55	53	53	—	—
V93	42 F	60	57		—	—
V97	33 F	69	55		—	—
			Cyanotic			
V40	5 F	56	56	56	56	56
V41	11 M	59	51	50	49	48
V49	8 M	56	53	53	53	—
V71	26 F	54	52	52	49	—
V73	19 F	64	59	57	56	—
V74	5 M	64	60	52	52	—
V84	4 M	66	64	60	—	—
V94	3 M	68	59		—	—
V114	4 F	65	54	—	—	—

and the result is very encouraging. In 26 of the 31 with this pattern there was some improvement and in half of them it was very striking (Table VI, Fig. 2 and 6–9).

It is difficult to judge how soon this improvement starts because these patients, like others who have section of the right ventricle, show after operation (Fig. 6B) an increase in T inversion that only passes off gradually in the course of three to four months. But we are disappointed if there is no improvement after six months though it may be progressive sometimes for two or even three years: we hardly expect improvement unless it has started within a year.

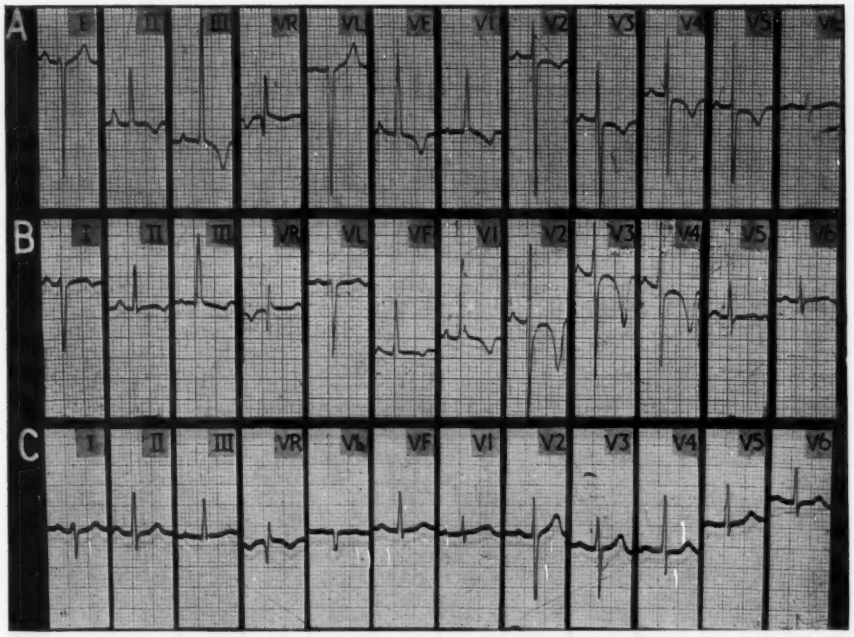


FIG. 6.—Disappearance of right ventricular strain and diminution of right preponderance from a girl, aged 7, with pulmonary stenosis and central cyanosis. (A) Before operation. (B) Three weeks after, showing much deeper T wave inversion in leads I, V2, V3, and V4. (C) Four years after, showing disappearance of all T wave inversion and much less right ventricular preponderance. Case V23 (H115).

TABLE VI

DIMINUTION OR RIGHT VENTRICULAR STRAIN AFTER VALVOTOMY IN SIMPLE PULMONARY STENOSIS

	Right ventricular strain			
	Greatly improved	Improved	Not improved	No R.V. strain
P.V.S. (pure) (28 cases) ..	8	7	4*	9
P.V.S. with P.F.O. (16 cases)	5	6	1*	4
P.V.S. (all 44 cases) ..	13	13	5	13

* One in each of these groups had a very good result clinically.

The cyanotic and acyanotic patients were analysed separately but as there seemed to be no difference the results have been combined. Of the 44 patients with records over a long enough time, 13 showed no right ventricular strain before operation, leaving 31 for consideration. Thirteen of these showed striking changes, the deep T inversion having disappeared or moved from V4 to V1 or from V5 to V2 or more (see Fig. 6–9); the result was exceptionally good in two where in addition to the disappearance of the T inversion, there was an unusual decrease in the right ventricular preponderance (see Fig. 2 and 6). All these have obtained excellent results clinically. Eight others improved but less than this, the T inversion having shifted one or two leads further to the right only or having become biphasic or late-rising instead of inverted (Fig. 8 and Fig. 8 of Campbell, 1954). One of these was disappointing at first in that her clinical result was excellent but the T inversion had only spread back from V4 to V3 after three years; after four years, however, there was further improvement and T was only biphasic in V2 and late rising in V3 (Case V39).

In three patients, however, the change was less than hoped for, the T inversion disappearing from V4 but still being present as far as V3. One of these has a good clinical result and has been followed for a year only but it may be her age of 40 years that prevents more change (Case V93). One is a good result clinically and her very large heart (c.t.r. 69) has become smaller, but she was 29 and it may be that the operation was too late or not complete enough to get a reversal of the right ventricular strain (Case V45). In the third, operation was advised only because of his high right ventricular pressure and right ventricular strain: the former has fallen from 110 to 55 and it is, therefore, disappointing that after two years he has shown no more cardiographic change (Case V92). Two others were difficult to assess, as they had complete right bundle branch block but the T inversion does not now spread so far across the chest leads.

There were only 5 cases where there was little or no improvement and two of these were among those with poor results clinically. In one with a good result (Case V49) T was inverted to V4 before operation and still is, though rather less so, and the slightly biphasic T in V5 and V6 has disappeared. The second achieved a good result clinically and there had been T inversion across to V6: perhaps

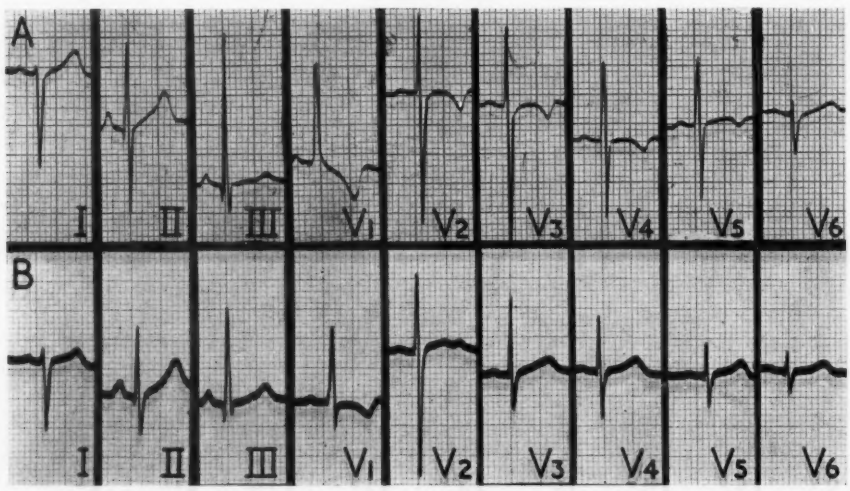


FIG. 7.—Considerable improvement in T inversion three years after valvotomy for acyanotic pulmonary stenosis. (A) Before operation, T sharply inverted from V1 to V4 and slightly in V5. (B) Three years after, T is less inverted in V1 and upright in all other chest leads, though notched in V2. The Q/R ratio in VR was 1 instead of 1/4. The standardization in the chest leads is 1 mV=0·5 cm. Case V30 (P247).

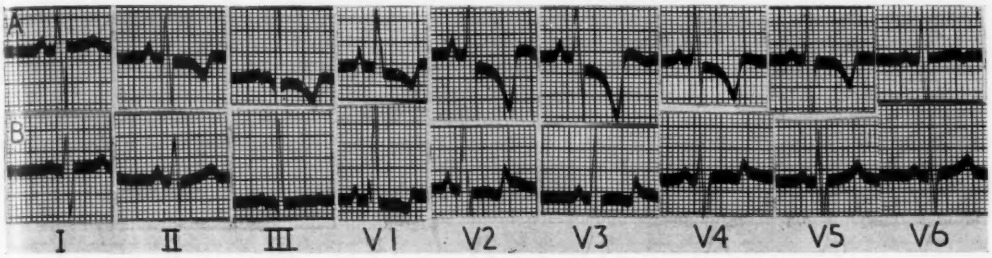


FIG. 8.—Great diminution of right ventricular strain after valvotomy for acyanotic pulmonary stenosis. (A) Before operation, with deep T inversion in leads II and III and from V1 to V5. (B) One year after operation, no longer showing the T waves inverted though they are still late rising (wing-shaped) in V1–V4. Case V88 (H356).

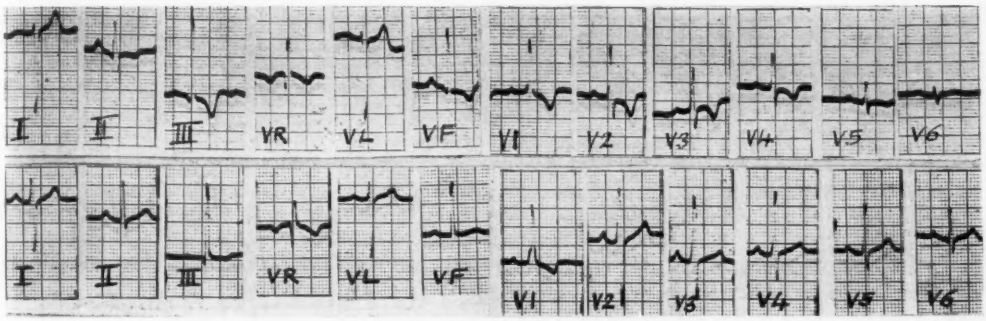


FIG. 9.—Disappearance of the pattern of right ventricular strain after valvotomy for acyanotic pulmonary stenosis. (A) Standard and chest leads before operation. (B) One year after operation. The improvement is even greater than appears, for the standardization of the chest leads in (A) is 1 mV=0·5 cm. Case V58 (P274).

because she was 25 years old, or perhaps because she has so far been followed only for a year there has been no improvement (Case V105). One patient with pulmonary regurgitation already referred to showed no change, T remaining inverted to V3. The last two were poor results clinically: in one a slight increase of right ventricular strain, T becoming inverted to V2, confirmed the clinical judgment (Case V80) and in the other (V104) bundle branch block developed during operation and persisted.

RIGHT VENTRICULAR PRESSURE

Pulmonary valvotomy is very effective in reducing the systolic pressure in the right ventricle: in all the 24 patients when catheterization was repeated after operation it was reduced to less than half of its previous level. The average pressure gradient fell to a third, from 122 to 42 mm.

In the 9 cyanotic cases the average change was a fall from 151/6 to 50/4 mm. with a pressure gradient of 32 mm. This reduction took place with little change in the pulmonary arterial pressure which rose only from 14/6 to 18/7 mm. Two (Cases V23 and V78) showed a fall to normal and most systolic pressures fell to between 45 and 60 mm. (Table VII).

Equally important, the right-to-left shunt was reduced and generally abolished, but in two (Cases V7 and V59) a much smaller shunt persisted. On the average, the O_2 saturation in the

TABLE VII

PHYSIOLOGICAL DATA IN CYANOTIC PULMONARY VALVE STENOSIS BEFORE AND AFTER VALVOTOMY

Case No.	Age and sex	Pressure in mm. Hg				Arterial O_2 saturation per cent		Pulmonary blood flow in l./min.		Right-to-left shunt as percentage of systemic flow		Clinical result
		Right ventricle		Pulmonary artery								
		Before	After	Before	After	Before	After	Before	After	Before	After	
V7	26 F	85*	—	11*	—	69	85	1·4	3·5	53	23	V. good
V23	11 F	45*	23/0	4*	12/4	68	92	1·5	3·0	54	0	V. good
V41	11 M	56*	20* (60/0)	9*	9* (14/5)	85	97	—	4·8	—	0	V. good
V47	7 F	180/8	58/6	20/7	28/11	84	96	2·7	4·7	30	0	V. good
V59†	20 M	240/12	48/10	10*	15*	60	89	1·1	2·0	62	35	V. good
V73	19 F	144/5	65/3	13/8	21/9	90	96	2·0	5·6	17	0	Good
V78	7 F	46*	31/0	19*	19/6	89	98	2·7	5·3	23	0	Good
V94	3 M	115/35	—‡	16/8	—	68	99	0·8	—	50	0	V. good
V95	33 F	110/5	46/2	9/3	15/7	90	94	(7·8)	5·0	24	0	Good

* Mean pressures. † Case 7 of Soulié *et al.* (1952). ‡ R.A. pressure had fallen from 15/5 to 7/5.

systemic arterial blood rose from 78 to 94 per cent; and the right-to-left shunt, expressed as a percentage of the systemic flow, fell from 37 to 5 per cent. Partly because of this and partly because of the reduced resistance at the pulmonary valve, the pulmonary flow increased from 2·5 to 4·2 litres a minute.

The 15 acyanotic patients showed very similar results. The average right ventricular pressure fell from 135/2 to 62/1 mm. with a pressure gradient of 44·5 mm. and, as before, there was only a small increase in the pulmonary arterial pressure from 14/7 to 17·5/7 mm. (Table VIII). None showed a normal right ventricular systolic pressure but in most patients it was between 40 and 65 mm. There was, of course, no right-to-left shunt to be abolished and the arterial O_2 saturation was not much changed (97·5 instead of 96%). The increase in the pulmonary flow was less than in the cyanotic cases (average 5·2 instead of 4·6 litres a minute).

In both groups the right ventricular pressure is generally between one-half and one-third of what it was before operation. It is disappointing that it does not fall to normal and that there is still some degree of pulmonary stenosis. This is, however, slight instead of severe and gives rise to few, if any, symptoms and does not seem likely to do so. Possibly, the valve itself has been divided as much as is possible and the presence of the stenosis has led to some underdevelopment of the area round it and of the outflow tract of the right ventricle. It does not seem desirable that the surgeon should make greater efforts to split the pulmonary valve by the closed method as this would probably increase the risk of pulmonary regurgitation, which is a serious though uncommon complication that every effort should be made to avoid.

Perhaps the pressure gradient is the most satisfactory way of expressing the result. In three cases it was below 14 mm. after operation; in ten it was between 25 and 39 mm.; in five it was between 40 and 49 mm. All these had good results except one with a pressure gradient of 45 mm. (Case V80). In four it was still higher, above 50 mm. In the first two of these, both excellent clinical results, it was 60 instead of 130 before operation (Case V43) and 78 instead of 158 (Case V30) and in both the right ventricular strain was reduced (Fig. 7). The third (Case V45) was improved, her heart became smaller, the right ventricular strain less, and the pressure gradient fell from 88 (mean) to 21 (mean) but the systolic pressure still showed a gradient of 94 mm. These three were all early cases. The fourth (Case V108) was one of the failures although the gradient was reduced from 173

TABLE VIII

PHYSIOLOGICAL DATA IN ACYANOTIC PULMONARY VALVE STENOSIS BEFORE AND AFTER VALVOTOMY

Case No.	Age and sex	Pressure in mm. Hg				Arterial O_2 saturation percentage		Pulmonary blood flow in l./min.		Result
		Right ventricle		Pulmonary artery						
		Before	After	Before	After	Before	After	Before	After	
V30	12 M	180/5	102/9	22/10	24/7	97	99	4·0	3·9	Good
V43	18 M	150/8	80/2	—	20/7	98	97	5·0	3·9	Good
V45	29 F	98* / —	30* / 110/6	10* / —	9* / 18/5	93	98	3·3	3·8	Good
V56	23 M	114/0	65/5	16/4	16/7	99	98	5·4	4·3	Good
V64	19 F	160/0	53/−4	—	15/4	95	98	3·8	5·2	Good
V70	13 M	140/5	65/2	16/10	18/8	99	97	3·7	6·7	Good
V80	25 F	112/−4	55/0	3/1	10/−4	94	94	4·6	5·0	Fair
V83	19 F	124/2	46/−3	10/6	14/4	97	96	5·2	5·9	Good
V88	11 M	150/0	50/−2	—	16/7	94	94	4·8	5·0	Good
V89	12 F	105/4	46/3	15/8	15/11	97	99	4·6	6·4	V. good
V92	25 M	110/0	55/−2	10/4	16/5	92	98	(6·0)	7·3	Good
V100	12 M	100/2	50/0	15/7	22/10	98	98	5·1	5·3	Good
V108	33 M	190/12	107/5	—	17/10	96	99	3·5	4·1	Poor
V118	20 F	121/0	39/1	18/9	25/7	99	99	(7·9)	3·8	Good
V116	21 M	170/−3		15/3		98		3·9		Good
V121	10 F	130/4	62/0	25/14	12/3	99	99	3·1	3·0	Fair

to 90 mm. Probably this failure should be attributed to the large degree of obstruction still remaining, and the third patient would also have been better if the stenosis had been relieved more completely.

PRESSURE CHANGES AT THE TIME OF OPERATION

Since October, 1951, the pressures in the right ventricle and pulmonary trunk have been recorded during operation, both before and after valvotomy, in as many patients as possible (Table IX). The results are difficult to interpret because the pressure has often fallen greatly from the effects of anæsthesia and operation and the state of the patient may have changed between the two readings and methedrine may have been injected. Generally, when figures before operation can be compared, the right ventricular systolic pressure had fallen to less than half, but sometimes it was better maintained, e.g. 120 compared with 150, and 97 compared with 112 mm. Hg.

In many of the earlier cases the results looked disappointing even when the valvotomy seemed successful and where later there was no doubt about the clinical improvement. In Case V70 for example, the right ventricular pressure fell from 95 to 85 mm. Hg only and yet catheterization a year after showed that it had fallen from 140 to 65 mm. Even when the fall of pressure was not great, the pulse waves were often much better in the pulmonary tracings. There were, however, other readings that measured the improvement better; in Case V73, for example, the systolic pressure fell from 73 to 48 in the right ventricle and rose from 6 to 15 mm. in the pulmonary trunk.

More recently, probably because of technical improvements in the recording for there is no evidence that the clinical results have become better, the pressure gradient across the stenosis has been greatly reduced more often. In ten consecutive cases, the average figures were 80/5 and 16/8 before operation and 48/3 and 19/8 mm. afterwards—a considerable fall in the pressure gradient—but even recently the records during operation have not always recorded the improvement that followed (Cases V116 and V121).

Few records show much rise in pulmonary pressure, but in a few it rose to about 30 mm. In

TABLE IX

PRESSURE FINDINGS BEFORE AND AFTER VALVOTOMY

Case No.	Catheterization before operation		During operation				Catheterization after operation	
			Before valvotomy		After valvotomy			
	R.V.	P.A.	R.V.	P.A.	R.V.	P.A.	R.V.	P.A.
V70	140/5	16/10	95/7	18/11	85/7	18/10	65/2	18/8
V73	144/5	13/7	73/0	6/0	48/0	15/7	63/3	21/9
V74	—	—	148/	—	70/0	40/24	—	—
V75	170/7	10/7	78/12	13/	30/7	21/13	—	—
V76	155/0	24/7	60/5	10/6	47/5	14/7	—	—
V78	46m.	17m.	97/5	14/6	94/9	16/10	31/0	19/6
V79	90/4	16/9	41/4	15/9	32/6	15/11	—	—
V80	112/−4	3/1	38/2	5/1	21/5	11/7	55/0	10/2
V83	120/2	10/6	60/5	12/7	60/10	15/	46/−3	14/4
V87	148/3	15/6	67/7	14/9	77/7	19/12	—	—
V88	105/4	14/8	60/8	24/12	44/6	36/10	46/3	15/11
V90	140/5	15/6	30/4	12/6	36/4	14/6	—	—
V92	110/0	10/4	55/3	12/8	45/0	15/8	55/2	16/5
V93	165/3	—	80/2	10/2	35/3	15/4	—	—
V94	115/35	—	55/15	8/6	50/7	30/15	—	—
V95	110/5	9/3	55/0	5/1	45/0	10/3	46/2	15/7
V97	160/10	36/15	110/0	25/9	53/0	21/13	—	—
V98	238/12	22/10	85/10	26/21	72/5	25/15	—	—
V100	120/0	15/7	89/0	23/7	55/0	16/2	51/0	22/10
V101	146/5	22/7	44/6	18/11	29/9	24/14	—	—
V104	112/−5	25/10	97/0	—	55/0	20/3	—	—
V105	150/0	15/3	120/10	13/9	72/10	21/14	—	—
V107	—	—	63/5	6/4	15/0	7/1	—	—
V108	190/10	—	80/8	5/3	54/8	16/11	107/5	17/10
V114	139/5	15/5	100/25	11 m.	43/15	25/6	—	—
V116	170/−3	15/3	110/2	14/1	110/5	25/2	—	—
V118	121/0	18/9	73/0	11/4	35/0	20/6	39/1	25/7
V120	157/2	12/3	150/2	22/8	104/10	20/10	—	—
V121	130/4	25/4	70/1	26/13	74/0	35/18	62/0	12/3

Case V88 it rose to 36/10 from 24/12 before valvotomy. Catheterization some months after operation, however, showed that while the operative and post-operative records of the right ventricular pressure are the same, 44/6 and 46/3, the pressure in the pulmonary trunk has fallen from the figure of 36/10 obtained at operation to 15/11, which is almost identical with her pressure at catheterization before operation, when it was 14/8 with a right ventricular pressure of 105/4 mm. Although these pressure measurements during operation help to tell if the valvotomy has been carried out completely enough, they can not be taken as good evidence of how much the right ventricular pressure has been reduced permanently.

PULMONARY STENOSIS AND A PATENT DUCTUS ARTERIOSUS

Not many cases of pulmonary stenosis with a closed ventricular septum and patent ductus arteriosus have been reported, and the following patient is, therefore, of interest because she got on well till she was 36 and has been successfully cured of both her lesions. She is also an epitome of three stages in the treatment of congenital heart disease, the avoidance of all activity, a life of reasonable activity, and modern surgical treatment.

Mrs. W. T. (Case V97), aged 29, was first seen in 1946. Heart disease had been diagnosed when she was 18 months old and the doctor never allowed her to go to school because of this. When she was 15, a new

doctor told her to do more and she began to lead an active life, only a little more breathless than her friends, and was able to work in hospital as an assistant nurse during the war. Later she married and could lead a normal quiet life.

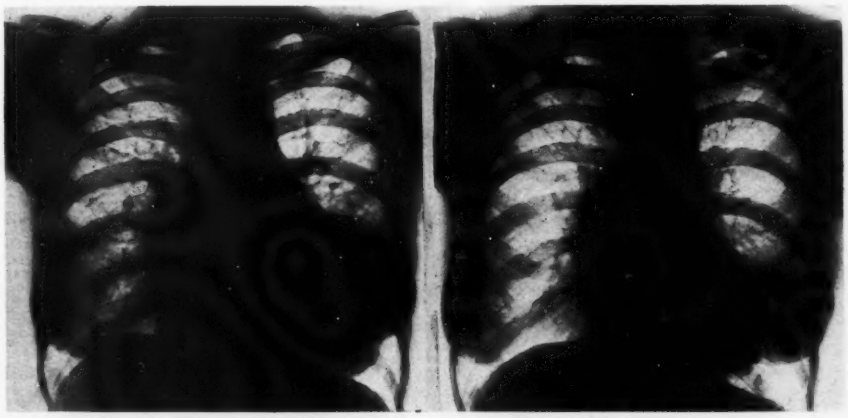
She had always had high coloured cheeks with some peripheral cyanosis with cold weather. The heart was very large (c.t.r. 66%), and on screening this seemed to be mainly the right ventricle: the pulsation was less than usual for a large ductus. There was a characteristic continuous murmur and thrill in the upper half of the left chest and the blood pressure was 145/65. The cardiogram showed right ventricular preponderance and a large R (14 mm.) in V1 with no S wave: T was inverted in leads III and V1 to V3. This and the peripheral cyanosis indicated something as well as a ductus, and Dr. Terence East thought that she had pulmonary stenosis, and that there was an independent systolic murmur rather lower down. She was anxious to have a child but was advised against this, and adopted a baby the following year.

Five years later she was admitted for investigations. She could do all her ordinary housework and could walk 5 miles. The physical signs were unchanged. The arterial blood was fully saturated and the oxygen saturation rose from 59 in the right ventricle to 85 per cent in the pulmonary artery. The pressure in the right ventricle was very high, 158/10, and that in the pulmonary artery was only 36/16 mm. The systolic pressure in the brachial artery was 134 at the same time, further evidence of a closed ventricular septum. The flow through the ductus was about two-thirds of the output of the left ventricle. The diagnosis of a patent ductus arteriosus and pulmonary stenosis was confirmed.

Though both these lesions could be cured by surgery, it seemed that with her age and her large heart the risk would be considerable, and as she had kept well without any further increase in heart size during these five years it was thought reasonable to delay a decision.

She was seen again two years later, when she was 36, and had been losing ground progressively for a year. The heart had become still larger with a c.t.r. of 69 per cent (Fig. 10) and the T waves were now inverted in V4. Now she had started losing ground it seemed likely to continue and that unless she had an operation soon it would never be possible.

Pulmonary valvotomy and closure of the ductus were, therefore, performed and were not specially difficult. Six months later she was enormously better. She was doing all her heavy housework without symptoms; she had walked five miles without fatigue and felt herself as well as she had when she was at work during the war. The heart had become much smaller (c.t.r. 59%) than it had been at any time since she first came under observation. A year later, she had taken on work at a school as well as her



A B

FIG. 10.—Enormous reduction in the size of the heart after operation in a patient of 35 who had simple pulmonary valvular stenosis and a patent ductuc arteriosus. (A) Before operation. The heart was very large (c.t.r. 69%: 17·2/24·8 cm.) and had been nearly as large as this for at least 7 years and perhaps much longer. (B) One year after, showing a great reduction in the size of the heart (c.t.r. 55 %: m.t.d. 13·6/24·8 cm.) with corresponding clinical improvement. Case V97 (O532).

household duties and was without any symptoms. She looks younger and her heart has decreased further (c.t.r. 55%) (Fig. 10). Her cardiogram has improved and the T waves are now upright in V4 and less inverted in V2 and V3.

Discussion

Many patients with simple pulmonary stenosis do not need operation and get on well for years. It is, however, not always easy to judge when it is becoming serious for there may be severe stenosis with few symptoms.

In an attempt to find which features are most helpful in judging the prognosis and the need for operation, we have compared four findings in a large group of cases—moderately severe or progressive symptoms, a large heart with a cardiothoracic ratio of 54 per cent or above, the pattern of T inversion across the chest leads, generally to V4, and a systolic right ventricular pressure of over 100 mm. Hg. Nearly half the severe cases that have been investigated show all these features so do not help to decide their relative significance. The only other group of any size consists of cases with all these features except the large heart, which shows that this is one of the later and more serious signs. There are also several cases with right ventricular pressure of over 100 mm. but with little in the way of symptoms. It seems clear that by the time the symptoms are severe or the heart much enlarged, the best time for operation has passed, though the results can still be excellent.

Kirklin *et al.* (1953) and Blount *et al.* (1954) have suggested that a right ventricular pressure over 75 mm. is an indication for operation regardless of symptoms. This may be so but we think it wiser not to accept this until more patients have been followed for a longer period after catheterization. Empirically, we have used a level of 100 mm. Hg.

Although catheterization should be widely used at present to establish more certain standards, we think that the electrocardiogram is of great value and provides the most decisive criterion. The patient without right ventricular preponderance has trivial stenosis and is unlikely to need operation at any time, but the patient with right ventricular preponderance should be watched for the development of strain. The pattern with deep T inversion in V3 (and still more if this spreads further to the right, as it often does even in patients with few symptoms) is probably the best indication for operation, as was suggested by Marquis (1951). Many of the patients dealt with here have, however, reached a much later stage and should in the future be operated on earlier.

Since Brock and Campbell (1950) first reported the results of valvotomy in simple pulmonary stenosis, many papers have been written confirming the good results obtained, but most of the series are small and have not yet been followed for long. Galligan *et al.* (1952) reported operation on 11 patients, all acyanotic, of whom one died. Kirklin *et al.* (1953) reported the results in 12 patients, of whom two died: they found that although the right ventricular pressure fell quickly it might not reach a normal level for some months, and thought that sometimes there was infundibular obstruction due to hypertrophy of the right ventricular muscle—a state of affairs that has sometimes been very evident post mortem. Therkelson (1953) reported operations on 12 patients, one of whom died and one of whom had a patent ductus also, but thought the follow-up period too short for valid conclusions. Humphreys *et al.* (1954) reported the results in 9 patients, most of whom were improved.

Dodrill *et al.* (1953) in describing a single operation under direct vision say that as time passes the pressure in the right ventricle may rise again, but their only reference for this is a personal communication of Lurie and Shumacker. In the discussion that followed their paper Lam stated that post-operative catheterizations had shown good results in all his twelve uncomplicated cases, but Schumacker said that his results had been disappointing in that there is only a slight fall in 5 patients and a large fall in 2, without a return to normal level in any. No doubt those with only a small fall would have been better with a more adequate operation and Humphreys pointed out that poor results might be due to this as he had found measuring the pressures at operation that his first attempt had not always been entirely effective.

A larger and more detailed series of 33 cases was reported by Soulié and Vernant (1954): only two died and most of the others obtained good results clinically without much change in the physical signs. Generally, the heart did not become much smaller and the cardiogram did not change much, though they publish one record where deep T inversion from V1 to V5 was replaced by small upright, but still late-rising, T waves. These are the views expressed by Heim de Balsac and Escalle (1954) also and by Durand and Metianu (1954). Soulié *et al.* (1952) had already reported the results of catheterization one to nine months after operation in 9 of these cases. The average fall in the right ventricular systolic pressure was from 160 to 108 mm. Hg—rather less than in our cases. They found the fall was small in 5, moderate in 2, and large in 2 cases. The pressure in the pulmonary artery rose " mais cette augmentation reste toujours très modérée et sans rapport avec le degré de la chute de pression ventriculaire droite " (Soulié and Vernant, 1954).

Dubost and D'Allaines (1954) have used the pulmonary arterial route and discuss this in detail: there were 4 deaths among 25 cases and the late results were said to be comparable with those achieved by the transventricular method. Sondergaard (1953) has also used this method in three cases.

Hosier, Pitts, and Taussig (1954) report the results in 86 patients, 7 of whom died: 4 of these had had a subclavian-pulmonary anastomosis previously, and these accounted for 2 of the deaths. Sixty-nine patients had been followed for up to 4 years, and most of them were improved. Nearly half showed a decrease in heart size and more than half showed some reduction in right ventricular strain. Catheterization had been carried out in 17 before and after operation. But these comments are taken from a short summary only and the full paper has not been seen. It sounds, however, as if their results are very similar to those we have described.

Blount *et al.* (1954) have described the results in 15 patients operated on in the usual way up to 1953 and 5 patients operated on since through a pulmonary arterial approach under hypothermia. Five patients of each group had catheterization repeated after operation. In the former the average right ventricular systolic pressure fell from 168 to 65 mm., with a small rise in the pulmonary arterial pressure from 16/10 to 22/10 mm.—figures that are very similar to ours in both respects. In the latter group who had open operations under hypothermia, the average pressure fell from 116 to a normal figure of 28 mm. and the pulmonary arterial pressure rose from 19/10 to 23/7 mm.

At first sight these results seem even better, but although none of their five patients died, operations under hypothermia can not yet be regarded as equally safe, and further there was a high incidence of pulmonary regurgitation, which they dismiss lightly. In the first group only one patient is stated to have developed a pulmonary diastolic murmur, but in the second group who had open operation at least four or perhaps all five patients did so. It is not clear how frequently the heart became larger, but this seems to have been common and they state: " The increase in heart size was more pronounced in the patients treated by wide excision of the pulmonic valve, and the murmur of pulmonic insufficiency was of greater intensity in these patients." In general, slight stenosis of the aortic or pulmonary valve is less serious than slight incompetence: their theoretical arguments that pulmonary incompetence is not so important remain to be proved and it can be a serious lesion. This production of significant regurgitation may, however, be the result of doing too much to the valve and may be avoided in future.

The case for transarterial valvotomy under hypothermia is as yet unproven and must await a larger series in which the mortality and results can be compared with the larger number done by the transventricular route. It is, for instance, uncertain that the pressure gradient can be corrected completely when the valve is thick, fibrous, and rigid. Although none of their five patients died, operations under hypothermia can not yet be regarded as equally safe, and most of the deaths in our series were in severely ill patients with a large heart in whom ventricular fibrillation developed early in the operation: these are just the type of case in which hypothermia is likely to prove dangerous. If operation needs to be repeated because it has been unsuccessful, the transarterial route would seem preferable.

Summary

Pulmonary valvotomy is a safe and successful treatment for simple pulmonary stenosis with a closed ventricular septum, when this is severe enough to need it. The 58 patients treated at Guy's Hospital have been followed and reported fully and 34 others gave similar results, making 92 in all.

In cyanotic cases the shunt can always be lessened and generally abolished. The average arterial O_2 saturation in our cases rose from 78 to 94 per cent and with this the polycythæmia disappeared: the pulmonary flow was increased from 2·5 to 4·2 litres a minute. In other particulars the cyanotic and acyanotic cases can be considered together.

Omitting the early very severe cases there have been only three deaths among 52 consecutive cases—less than 6 per cent. The clinical results are good in 46 of the 50 who survived operation and disappointing in 4 patients only.

This clinical impression is supported by improvement in physical findings. When the heart is enlarged it generally becomes smaller: the average decrease was nearly 10 per cent, the cardio-thoracic ratio falling from 60 to 54 per cent. When there is electrocardiographic evidence of right ventricular strain this often becomes less and sometimes disappears entirely, and the signs of right ventricular preponderance become less. Reversal of the pattern of right ventricular strain can not be promised always, especially if it has been present for a long time or if the heart is large.

Valvotomy for simple pulmonary stenosis is, therefore, a more satisfactory operation than either direct or anastomotic operations for Fallot's tetralogy for it more nearly achieves the ideal of restoring the heart to normal. It does not quite achieve this but converts the pulmonary stenosis from a severe to a slighter degree that generally does not seem of great importance.

In the 24 cases that have had catheterization repeated since their operation, all have shown a great reduction of the right ventricular systolic pressure—never to less than one-half and generally to about one-third of what it was before. Two have shown a fall to a normal pressure. The increase in the pulmonary arterial pressure is much smaller but the pressure gradient is on the average reduced from 122 to 42 mm.

None of these patients has shown any evidence of the stenosis becoming more severe again during the period of observation. Several have been followed for four years and one who was incapacitated before operation remains just as well and is leading an active life six years later.

We are greatly indebted to Dr. D. Deuchar for the earlier and Dr. R. Shephard for the later catheterization reults, and to the Registrars of the National Heart Hospital for those of Cases 23, 80, and 88. We should also like to thank Dr. Charles Baker for referring Cases 75, 93, and 104, Dr. James Brown for Case 86, Dr. Frances Gardner for Case 78, and Professor Soulié for Case 59, and to thank the two latter for the results of catheterization also.

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UPPER ATRIO-VENTRICULAR NODAL BEATS PRECIPITATED BY VENTRICULAR EXTRASYSTOLES WITH RETROGRADE CONDUCTION

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The arrhythmias observed in the cases to be described show combinations of rare features which to our knowledge have not hitherto been recorded.

CASE 1

The patient was a 75-year-old man with a four years' history of nocturnal attacks of cardiac asthma, increasing dyspnœa, and œdema of the feet. On admission he was found to be suffering from hypertensive cardiac failure. The blood pressure was 210/120 mm. Hg. The heart action was regular, rate 112. Radiological examination showed enlargement of the heart with evidence of pulmonary congestion. Prior to admission the patient had not received any medication. In the course of three-and-a-half weeks stay in hospital treatment included digoxin, 0·25 mg. twice daily, mersalyl injections, 2 ml. twice weekly, and aminophylline, 3 grains thrice daily. His condition improved considerably.

A routine electrocardiogram taken three days after admission (Fig. 1) showed sinus rhythm with a fairly constant cycle length of 0·76 sec. (rate 78), P–R intervals of 0·16 sec., left ventricular strain, and ventricular extrasystoles. Their shape varied somewhat owing to the effect of digitalis, and to distortion of P waves (see below). Their coupling varied between 0·42 and 0·68 sec. Some of the extrasystoles showed a sharply inverted P′ wave in their final deflection in leads II and III, indicating retrograde conduction to the auricles.* The P waves of the first post-extrasystolic beats after such extrasystoles were sharply inverted in leads II and III and the P–R intervals measured only 0·12 sec., whereas the P waves of the post-extrasystolic beats after ventricular extrasystoles without retrograde conduction were identical with those of other sinus beats. (The P wave of the last post-extrasystolic beat in lead III was actually a fusion beat between a sinus P wave due at the time and a sharply inverted P wave; this could be ascertained from later records, see Fig. 2.)

In view of the great variations in the coupling of the extrasystoles, parasystole was suspected, but in longer records taken four days later, which showed even greater variations in coupling, a parasystolic mechanism could not be established. Instead, gradually decreasing couplings were found, whereby those extrasystoles falling comparatively early in diastole showed retrograde conduction to the auricles and were followed by a post-extrasystolic beat with inverted P waves in leads II and III and shortened P–R intervals.

Thus lead II (Fig. 2) showed at its beginning two sinus beats occurring at an interval of 0·86 sec. The following beat was a ventricular extrasystole with the long coupling of 0·74 sec., recorded at a time when most of the P wave of the next sinus beat had already been inscribed. This extrasystole did not show any features suggestive of retrograde conduction, and the following beat had a normal

* P waves, that are sharply inverted in leads II and III and are indicative of retrograde conduction of an extrasystole, are called P′ waves in this paper.

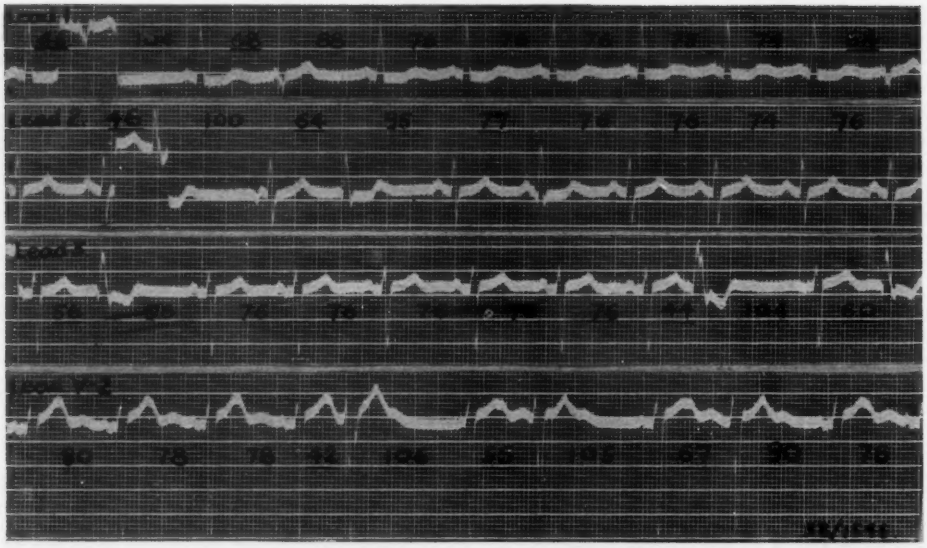

FIG. 1.—For explanation, see text. In this and the subsequent figures numbers indicate intervals in sec./100. Couplings of extrasystoles are underlined.

P wave, preceding the QRS complex at a P–R interval of 0·16 sec. The next beat was a ventricular extrasystole of essentially the same shape as the preceding one, except for some variation early in its final deflection produced by the P wave of the next sinus beat due at that time, but its coupling was only 0·65 sec. The first post-extrasystolic beat was a normal sinus beat. The post-extrasystolic intervals after these two extrasystoles were compensatory. The next extrasystole followed with the still shorter coupling of 0·56 sec.; at the foot of the descending limb of its R wave a P′ wave is visible, strongly suggestive of retrograde conduction. The first post-extrasystolic beat had a sharply inverted P wave, its P–R interval being shortened to 0·11 sec. Similar features were observed in the post-extrasystolic beat following the next extrasystole, whose coupling was only 0·40 sec. and which had also a P′ wave in its final deflection. The post-extrasystolic intervals after these last two extrasystoles were shorter than compensatory, the first only slightly, but the second falling short by about 0·15 sec. It is also significant that the interval between the P′ wave of the extrasystole and the following inverted P wave equals the cycle length of the sinus rhythm, namely 0·84 sec. As the first post-extrasystolic beats following, respectively, the last two extrasystoles have all the characteristics of upper atrio-ventricular nodal beats, it has to be concluded that the extrasystoles with retrograde conduction, and only these, precipitated a transient A-V rhythm. In lead II, this consisted of only one beat. The next beat (the second beat of the lower strip of lead II) showed a mainly upright P wave with a very small initial downward deflection. It differed in shape from the sinus P waves and its P–R interval was shortened to 0·11 sec., while the subsequent beats were normal sinus beats with P–R intervals of 0·16 sec. The P wave of this second post-extrasystolic beat has to be considered a fusion beat, intermediate in shape between the rounded upright sinus P waves and the sharply inverted P waves of upper A-V nodal beats.

Similar conditions were recorded in lead III. There were again four ventricular extrasystoles with decreasing coupling. The first two occurred after the longer couplings of 0·76 and 0·70 sec., respectively, did not show any features suggestive of retrograde conduction, and were followed after a compensatory pause by post-extrasystolic beats which were sinus beats with normal P waves and

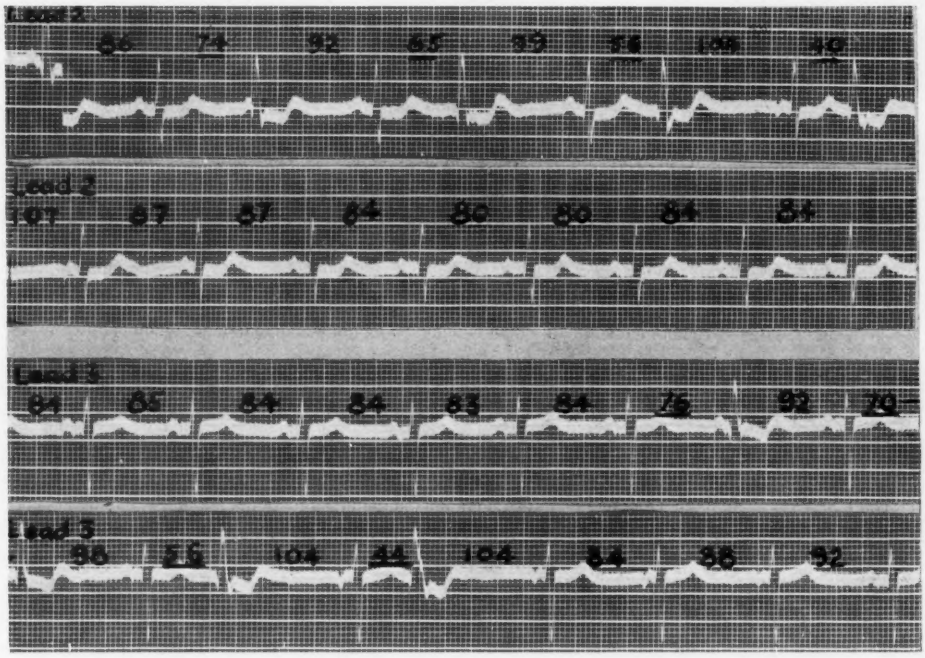

FIG. 2.—Recorded four days after Fig. 1. The two strips of leads II and III are continuous. Note gradually decreasing coupling of consecutive extrasystoles, retrograde conduction of extrasystoles falling early in diastole, and upper A-V nodal post-extrasystolic beats after these only. For further explanation, see text.

normal P–R intervals. The last two extrasystoles occurred with the shorter couplings of 0·56 and 0·44 sec., respectively, had P′ waves in their final deflections, and were followed, after an interval shorter than compensatory, by beats with sharply inverted P waves and shortened P–R intervals. The most noteworthy feature of this lead is that the last extrasystole with retrograde conduction was followed, not by one, but by three upper A-V nodal beats; subsequently sinus rhythm became re-established. The cycle lengths of the A-V nodal beats, measuring 0·84 and 0·88 sec., were very close to that of the sinus rhythm. Similar features were recorded in V4 (not shown). In this lead, one group of bigeminal rhythm was initiated by a fusion beat, with a ventricular complex intermediate in shape between that of the sinus beats and the extrasystoles, which had the unusually long coupling of 0·80 sec. The P′ waves were not distinct in any of the chest leads.

A further record (Fig. 3), taken six days after the preceding one and reproducing lead II and a longer strip of V1, showed that the arrhythmia had altered in several important respects. The rate of the sinus rhythm was unchanged, the cycle length being 0·80–0·84 sec. The two extrasystoles in lead II were recorded in a long period of undisturbed sinus rhythm. They had the comparatively short coupling of 0·44 sec., showed distinct P′ waves in their final deflections, but were followed after a compensatory post-extrasystolic interval by normal sinus beats. Contrary to the condition found six days earlier (Fig. 2), these beats did not precipitate A-V nodal beats. The time relations suggest that the retrograde impulse did not reach the S-A node, the dominant sinus rhythm thus remaining undisturbed.

In lead V1, altogether sixteen extrasystoles of the same shape were recorded, divided into two groups comprising five and eleven extrasystoles respectively, the two groups being separated by three

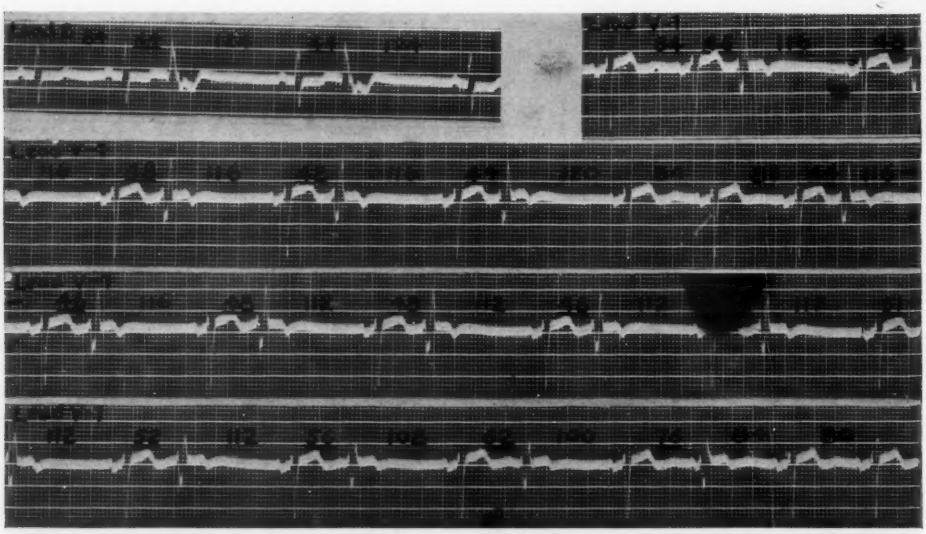

FIG. 3.—Recorded six days after Fig. 2. All strips of lead V1 are continuous. Lead II: Two extrasystoles with retrograde conduction followed after a compensatory pause by sinus beats. Lead V1: Practically constant coupling of the five extrasystoles of the first group, gradually increasing coupling in the second group of eleven extrasystoles.

successive sinus beats. The extrasystoles of the first group had couplings of 0·46, 0·48, 0·48, 0·48, 0·44 sec., i.e. varying only within such narrow limits that the coupling could be considered as constant. In the second group, the couplings of the extrasystoles gradually increased from 0·44 to 0·76 sec., the post-extrasystolic intervals being compensatory; subsequently sinus rhythm prevailed. Whether these extrasystoles were reversedly conducted to the auricles cannot be deduced from the tracing.

DISCUSSION

The records of this patient showed several unusual features which warrant some more detailed discussion, namely, (1) systematic variations in the coupling of the extrasystoles; (2) fairly accurate coupling on one occasion; (3) retrograde conduction of some of the ventricular extrasystoles; and (4) transient upper A-V nodal rhythm following only ventricular extrasystoles with retrograde conduction.

Variations in Coupling. A parasystolic mechanism could not be established. Instead, systematic changes in the lengths of coupling were found. In the first record, the couplings of consecutive extrasystoles increased before undisturbed sinus rhythm became re-established. In lead V2 (Fig. 1), this increase ranged from 0·42 to 0·67 sec.; in lead V4 (not shown), from 0·44 to 0·62, and in a subsequent bigeminal group from 0·48 to 0·64 sec. It is important to note that these changes in coupling occurred without any significant alteration in the sinus rate. This condition is uncommon. Examples have been described by Zander (1927), Mack and Langendorf (1950) (Case 1), Scherf and Schott (1953) (Fig. 130), and also form part of an observation by Goldenberg and Scherf (1928). Zander, and Mack and Langendorf believe that disturbances of conduction were responsible for the gradually increasing coupling. Goldenberg and Scherf, however, found this explanation unacceptable in their case and gave several reasons for this view. In the first place, they rejected Zander's assumption that retrograde conduction to the ectopic focus through the peripheral branch of the Purkinje system was completely blocked and the focus thus accessible only by delayed conduction in the orthograde direction; this is not consistent with experimental findings demonstrating that such retro-

grade conduction is preserved even in the presence of pronounced myocardial damage with grave impairment of orthograde conduction.

Furthermore, the long couplings in Goldenberg and Scherf's case, sometimes exceeding 0·80 sec., were cited by these authors as an argument against delay of conduction being the responsible factor. The same holds good for the present case. Couplings of 0·76 sec. were found twice, one of 0·77, and on one occasion one of 0·8 sec., producing a fusion beat, was recorded.

The most cogent reason is, however, that—as in Goldenberg and Scherf's case—the reverse phenomenon was also observed, namely, a gradual decrease in the coupling of consecutive extrasystoles. Thus, in lead II (Fig. 2), the couplings gradually decreased from 0·74 to 0·40 sec., in lead III from 0·76 to 0·44, and in V4 (not shown) from 0·76 to 0·40 and from 0·80 to 0·40 sec. in two separate groups, respectively. In the great majority of cases, the effect upon conduction of successive impulses traversing the same path consists in progressive delay in conduction. The reverse is only observed in comparatively rare exceptions (some instances of successive auricular extrasystoles or of paroxysmal tachycardia). For these reasons Goldenberg and Scherf (1928) assumed that, in their case, some disturbance of impulse formation was the underlying factor. This seems also the most acceptable explanation for the present case, as far as the variations in length of coupling are concerned.

Temporary Accurate Coupling. On one occasion (Fig. 3, lead V1), a group consisting of five successive bigeminal groups was recorded, with couplings of the extrasystoles of 0·46, 0·48, 0·48, 0·48, and 0·44 sec. This could be considered as within the range of accurate coupling. While not too much importance should be attached to this short period, it may be mentioned that accurate coupling at some time was also observed in most of the few comparable cases already quoted (Zander, 1927; Goldenberg and Scherf, 1928; Mack and Langendorf, 1950). If in the present case this short period is accepted as indicating temporary accurate coupling, this observation would be a further instance of the transition in the same case from extrasystoles with systematically varying coupling to those of the common variety with constant coupling. The change from ectopic beats with varying coupling to extrasystoles in the strict sense of the term, i.e. with accurate coupling, is altogether rare, even if the cases of transition from parasystole to extrasystoles are included (Scherf and Schott, 1930; Rothberger, 1931; Faltitschek and Scherf, 1932; Vedoya and Battini, 1939).

Retrograde Conduction of some of the Ventricular Extrasystoles. Retrograde conduction to the auricles of ventricular extrasystoles is indicated by a P′ wave, which is sharply inverted in leads II and III, following the QRS complex of the extrasystole at an interval compatible with retrograde conduction. The diagnosis is rendered more certain if extrasystoles without retrograde conduction are recorded in the same lead, so that their shape undistorted by P′ waves is available for comparison, and if the post-extrasystolic interval is not compensatory. Both these conditions prevail in the present case; and it can be shown that only those extrasystoles were reversedly conducted which occurred comparatively early in diastole, i.e. with shorter couplings. Thus, in leads II and III of Fig. 1, only two extrasystoles with couplings of 0·44 and 0·46 sec. showed retrograde conduction, whereas others with couplings ranging from 0·56 to 0·77 sec. did not demonstrate this phenomenon. Similarly, in leads II and III of Fig. 2, four extrasystoles with couplings ranging from 0·40 to 0·56 sec. were conducted to the auricles, whereas another four with couplings between 0·65 and 0·76 sec. were not.

A similar observation was made by Kistin and Landowne (1951), who established by means of œsophageal leads that the retrograde conduction of ventricular extrasystoles in man is far commoner than usually assumed. These authors point out that extrasystoles falling late in diastole tend to occur immediately before or after the P wave of the next sinus beat, that is, at a time when activation of the auricles by the next S-A impulse has started, which precludes retrograde activation. It is thus the extrasystoles with the shorter couplings which are most likely to show retrograde conduction.

Another possible factor may be the supernormal phase, namely the assumption that retrograde conduction takes place during the supernormal phase of conductivity of the preceding beat. This mechanism was suggested to account for the retrograde conduction in parasystole of ectopic beats with a comparatively short coupling to the preceding beat (Scherf and Schott, 1953). The order of length of the supernormal phase, which was found in some of the few cases in which its presence could be accepted as established in the human heart (e.g. Jervell, 1934; Froment *et al.*, 1939), is consistent with this assumption.

Transient Upper A-V Nodal Rhythm following only Ventricular Extrasystoles with Retrograde Conduction. In the standard leads, uncomplicated upper A-V nodal rhythm is characterized by ventricular complexes of

supra-ventricular shape, preceded at an abnormally short P–R interval by P waves which are low positive or iso-electric in lead I and sharply inverted in leads II and III. In some of the chest leads such P waves are also inverted. Post-extrasystolic beats following ventricular extrasystoles with retrograde conduction to the auricles and showing these characteristics are seen in Fig. 1 after the first extrasystole in leads II and V2, and in Fig. 2 after the third and fourth extrasystole in leads II and III. The post-extrasystolic intervals terminated by upper A-V nodal beats were shorter than compensatory. The interval between the P′ wave of the extrasystole and the inverted P wave of the first post-extrasystolic A-V nodal beat equalled, or was slightly (0·04 sec.) longer than the cycle length of the prevailing sinus rhythm. These time relations suggest that the retrograde conduction extended to the sinus node. A-V nodal post-extrasystolic beats were not observed after extrasystoles without retrograde conduction.

The post-extrasystolic intervals after extrasystoles with retrograde conduction being long, their termination by escape beats can be easily understood. The unusual feature about these beats is that they showed the characteristics of upper A-V nodal beats, with preceding activation of the auricles. In man, nodal escape beats are nearly always of the variety with simultaneous activation of auricles and ventricles. In the latter, P waves are either absent or, being buried in the ventricular complex, are recognizable only by some slight deformation of the QRS complex. It was emphasized by Scherf (1931) that in A-V nodal escape beats a P wave never precedes the ventricular complex. In the present case, transient upper A-V nodal rhythm extended at times over several beats. Thus, in Fig. 2, the last extrasystole in lead III was followed by three upper A-V nodal beats; and in lead II the second post-extrasystolic beat following the last extrasystole had a fusion P wave, intermediate in shape between the P waves of the sinus and the A-V nodal beats, and a shortened P–R interval.

We have been unable to find a comparable instance in previous work on the arrhythmias. The only case known to us, which shows this phenomenon, is the following unpublished observation of Scherf which he has kindly placed at our disposal to be included in this paper.

Case 2

The tracing (Fig. 4), recorded in a 63-year-old woman admitted to hospital for gall stones without any cardiac or other complications, demonstrated sinus rhythm with a cycle length of 1·04 sec. (rate 57), and ventricular extrasystoles which, in leads II and III, showed the characteristic P′ waves in the final deflections, indicating retrograde conduction. The first post-extrasystolic beat, following an interval far shorter than compensatory, had a flat diphasic P wave in lead II and a frankly inverted P wave in lead III. The P–R intervals of these post-extrasystolic beats were shortened to 0·08 sec. in lead II and 0·1 sec. in lead III, compared with P–R intervals of 0·12 and 0·12–0·14 sec. of the sinus beats in these two leads. The P′–P intervals measured 1·14 sec., that is, they exceeded the P–P intervals of the sinus rhythm by 0·1 sec. Although in the two chest leads P′ waves were not recognizable and the changes in the P waves of the post-extrasystolic beats were only very slight, the same conditions can be assumed, since the time relations (lengths of couplings and post-extrasystolic intervals) were identical. This is, therefore, a further instance of ventricular extrasystoles with retrograde conduction, in which the post-extrasystolic intervals were terminated by upper A-V nodal beats. No digitalis had been administered.

Mode of Origin of Transient Upper A-V Nodal Rhythm

The two observations described demonstrate the temporary precipitation of an upper A-V nodal rhythm by retrograde impulses, and by these only. In order to explain the preceding activation of the auricles, the assumption of any delay in conduction in the ventricles of the A-V nodal beats is not justified, since no evidence of disturbances of intra-ventricular conduction was present in the sinus beats. Moreover, the longer post-extrasystolic intervals created if anything better conditions for conduction.

The phenomenon can best be understood by assuming that the retrograde impulse of the ventricular extrasystole facilitated the conduction of the A-V nodal impulse in the auricles. Therefore, the interval between impulse formation in the A-V node and activation of the auricles was shorter than in the common variety of A-V nodal escape beats.

Experimentally, the importance of facilitation in retrograde conduction was established in dogs

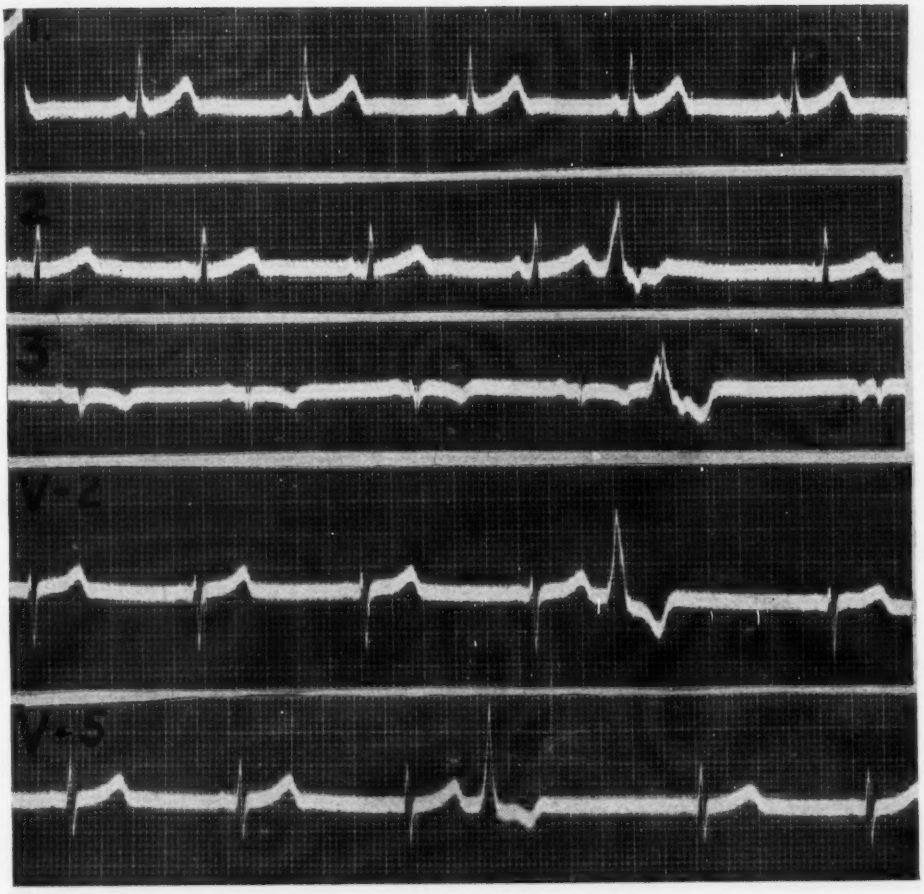

FIG. 4.—Ventricular extrasystoles with retrograde conduction, termination of post-extrasystolic intervals by upper A-V nodal beats. From another patient. Reproduced by courtesy of Dr. D. Scherf.

by Lewis and Oppenheimer (1911). They found that, if a ventricular rhythm was produced by means of induction shocks, the auricles responded to the ventricular beats only after a variable number of cycles. Clinically, this phenomenon has been shown in an observation by Allan (1926). During attacks of paroxysmal ventricular tachycardia, retrograde conduction to the auricles of every second beat became established only after several beats without such retrograde conduction had first occurred at the onset of these attacks.

SUMMARY

An unusual ectopic arrhythmia is described which showed ventricular extrasystoles with systematically increasing and at other times systematically decreasing coupling. Extrasystoles falling comparatively early in diastole showed signs of retrograde conduction to the auricles and only these were followed by upper A-V nodal post-extrasystolic beats.

In a second case the post-extrasystolic intervals after ventricular extrasystoles with retrograde conduction to the auricles were also terminated by upper A-V nodal beats.

Reasons are given for the view that the variations in coupling were due to disturbances in impulse formation and not to disturbances in impulse conduction.

Facilitation of conduction in the auricles of the A-V nodal post-extrasystolic beats is put forward as a tentative explanation for the occurrence of A-V nodal escape beats and temporary post-extrasystolic A-V nodal rhythm with preceding activation of the auricles.

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PATENT DUCTUS ARTERIOSUS WITH AN ABNORMAL AORTIC VALVE

BY

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In July, 1833, Dr. R. L. Nixon of Dublin was consulted by Dr. B., an English " medical gentleman," aged 27. " He was labouring under dyspepsia of rather an aggravated form, the result as he supposed of some alteration he had made during the preceding month in his usually very temperate habits." The aorta exhibited a " bruit de soufflet " through its whole course and beneath the anterior border of the liver was a pulsating mass. Dr. William Stokes was called and it was considered " that inflammation of the lining membrane of the aorta existed." In April, 1834, the patient died and Dr. Nixon demonstrated at necropsy that there was an aortic coarctation and a patent ductus arteriosus, but more remarkably, the aortic valve was " completely obliterated by an irregular fleshy mass. Several particles of phosphate of lime were deposited in the mass " (Nixon, 1834).

This is the first description we have discovered of aortic valve disease associated with a patent ductus arteriosus (P.D.A.). Hare (1859) described the post-mortem findings in a baby of six months, who had a bicuspid aortic valve and a P.D.A. Barie (1886) reported a patient with P.D.A., coarctation of the aorta, and aortic incompetence; in this case also the aortic valve lesion may have been a bicuspid valve. Morrison and Edwards (1950) described a patient who died when aged about twenty-six with a P.D.A. and a sub-aortic shelf in whom the aortic cusps were thickened and the commissures slightly fused. Gross and Longino (1951) made a clinical diagnosis of sub-aortic stenosis in three out of 412 patients operated on for P.D.A. and Burchell *et al.* (1953) add a further similar case among seven with P.D.A. and pulmonary hypertension. However, the certain clinical distinction between valvular and sub-aortic stenosis is impossible. Of 9 patients with congenital mitral stenosis reported by Ferencz *et al.* (1954) three had both aortic stenosis and a P.D.A. among other abnormalities.

Clinical Material

Eight cases are here reported of P.D.A. associated with aortic valve disease. They were found among about 190 cases of P.D.A. operated on at Great Ormond Street Hospital for Sick Children and St. Thomas' Hospital during the period 1947–53. This is a higher incidence than one would have expected in view of the sparse reference to this combination. The clinical and laboratory findings are therefore given in some detail.

That the P.D.A. was not the only abnormality present was evident in most of them before operation, but the exact nature of the complicating lesions was sometimes determined only after thoracotomy for ligation of the P.D.A. None of the patients have died.

Case Summaries

Case 1. G.P. (female). She remained well until the age of 17 months when she developed pneumonia and on examination by her own doctor was found to have an abnormal heart. At the age of 4 years she had subacute bacterial endocarditis following tooth extraction. Blood culture grew *Streptococcus viridans* and she was treated with penicillin and chloramphenicol at another hospital. Despite developing congestive cardiac failure she eventually made a good recovery.

A year later she was first seen at the Heart Clinic, Great Ormond Street. She was breathless on exertion. The præcordium bulged and the apex beat was abnormally forceful. There was marked arterial pulsation in the neck. A systolic thrill was felt on both sides of the sternum at the base, it was conducted up into the neck, and was accompanied by a systolic murmur with the same distribution. The blood pressure was 105/60 mm. X-rays (Fig. 1) showed enlargement of the left ventricle, increased pulsation in the aorta,

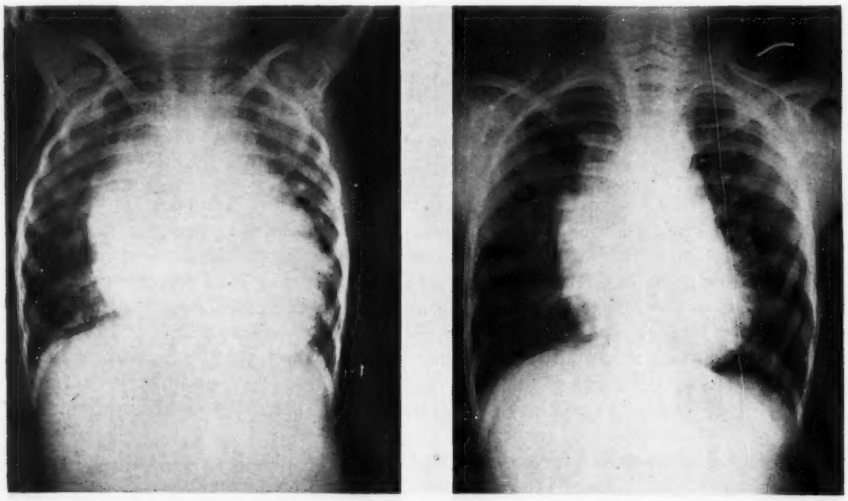


FIG. 1.—*Case* 1 before and after ligation of the patent ductus arteriosus, showing the decrease in heart size and pulmonary vascular markings after operation.

and increased pulmonary vascular markings. The electrocardiogram showed left ventricular hypertophy and on phonocardiography in the second left interspace the systolic murmur was seen to run up to the second sound which was followed by a short diastolic murmur. Six months later the murmurs in the pulmonary area had become continuous and at cardiac catheterization the catheter passed through a patent ductus arteriosus. At the age of six she was operated on and a short aneurysmal ductus was ligated.

After operation a systolic thrill and murmur were still present in the suprasternal notch; they radiated up into the neck and were both also noted at the apex; there was also an early diastolic murmur. X-rays (Fig. 1) showed a reduction in heart size and there was less left ventricular hypertrophy cardiographically. A phonocardiogram one year after operation confirmed the presence of systolic murmurs at both the base and apex and the early diastolic murmur.

Summary. Patent ductus arteriosus, aortic stenosis and incompetence.

Case 2. G. M. (male). No abnormality was found until routine examination at the age of five disclosed a cardiac murmur. He did not play games at school but gradually became able to walk quite long distances. He was admitted to Great Ormond Street Hospital when aged nine. He was underweight (40 lb.), under height (48 in.), and anæmic. The apex beat was in the sixth interspace in the mid-axillary line. There was a systolic murmur and thrill maximal in the third left interspace and conducted up into the neck. A diastolic murmur was heard to the right of the sternum. The blood pressure was 110/40. X-rays showed gross cardiac enlargement mainly of the left ventricle and there was dilatation and increased pulsation of the aorta. The pulmonary vascular markings were increased. The cardiogram showed left ventricular hypertrophy

and strain. At cardiac catheterization a left-sided superior vena cava was found and the catheter passed through a patent ductus arteriosus. Angiocardiography showed that there was also a right-sided superior vena cava. At the age of ten the ductus (15 mm. in diameter) was ligated.

After operation the pulse pressure remained high (130/40) and the cardiogram was unchanged. There was a systolic thrill and murmur and an early diastolic murmur in the second right interspace: these were demonstrated on phonocardiography. X-rays showed a slight decrease in the heart size and the pulmonary vascular markings returned to normal.

Summary. Patent ductus arteriosus, aortic stenosis and incompetence.

Case 3. R.Z. (male). At the eighth week of pregnancy, his mother had rubella. A cardiac murmur was heard at the age of six months. When aged 11 years he became short of breath on exertion and was first seen at Great Ormond Street Hospital. He had arachnodactyly and stippled retinæ. The præcordium bulged and the apex beat was in the anterior axillary line. There was a widespread præcordial systolic thrill conducted up into the neck, a loud systolic murmur in the third and fourth right intercostal spaces, and a continuous murmur in the pulmonary area. These murmurs were confirmed by phonocardiography, which showed the systolic murmur to be diamond shaped, and in addition a short diastolic murmur was seen at the apex. His blood pressure was 140/40. X-rays showed marked cardiac enlargement mainly of the left ventricle, and increased pulmonary vascular markings. The cardiogram showed left ventricular hypertrophy and strain. At cardiac catheterization the oxygen saturations were: right atrium and right ventricle 9·9 vols. per 100 ml., right main branch of pulmonary artery 12·1 vols per 100 ml., but the catheter did not enter a patent ductus. At thoracotomy at the age of twelve a large ductus, 20 mm. in diameter, entering the right main branch of the pulmonary artery, was ligated.

After operation his blood pressure was 90/50. There was a systolic thrill and systolic and early diastolic murmurs in the aortic area. X-rays showed a decrease in the heart size and the pulmonary vascular markings were now normal. The cardiogram remained unchanged.

Summary. Patent ductus arteriosus, aortic stenosis and incompetence.

Case 4. R.M. (male). He suffered from recurrent respiratory infections and epistaxes as an infant. At the age of two, a loud systolic murmur was heard. He was first seen at the Heart Clinic, Great Ormond Street, when seven, and had considerable dyspnœa on exertion. The apex beat was 3·7 cm. outside the nipple line. There was a systolic thrill and murmur in the aortic area conducted up into the neck and a continuous thrill and murmur in the pulmonary area. There was also an early diastolic murmur down the left sternal edge. These murmurs were confirmed by phonocardiography (Fig. 2A). His blood pressure was 110/55. X-rays showed enlargement of both ventricles, and enlargement of the pulmonary artery and its branches. The cardiogram indicated left ventricular hypertrophy. At cardiac catheterization the oxygen saturations in the right ventricle and pulmonary artery were 58 and 71 per cent respectively, but the catheter did not enter a ductus. At thoracotomy a vessel was ligated that was thought to be a ductus, but afterwards there was no change in the continuous murmur. It was thought that the left main branch of the pulmonary artery had probably been ligated in error and this conclusion was supported by finding much decreased vascular markings on the left side on screening. Four years later a further thoracotomy was done. The left main branch of the pulmonary artery was small and appeared to have no flow through it. A large ductus was found and ligated.

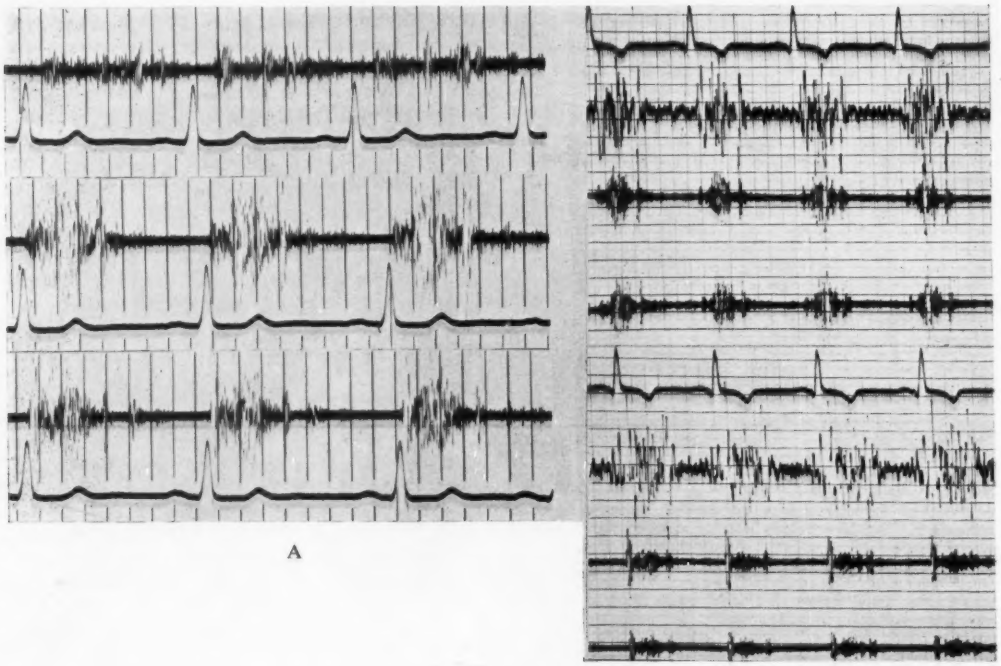
After operation he developed temporary congestive cardiac failure. On recovery his blood pressure was 110/80. There was a systolic thrill and murmur in the aortic area conducted into the neck and an early diastolic murmur down the left sternal edge (Fig. 2B). X-rays showed a decrease in the size and pulsation of the pulmonary vessels on the right side. The cardiogram showed no change.

Summary. Patent ductus arteriosus, aortic stenosis and incompetence.

Case 5. N.H. (male). His mother had rubella in the second month of pregnancy. He was known to have a heart lesion and bilateral cataracts at birth and after a few weeks was found to have bilateral deafness. During infancy he had recurrent chest infections. When first seen at St. Thomas' Hospital at the age of thirteen, he had slight dyspnœa on exertion and was undersized (weight 58 lb., height 57 in.). The left chest was prominent and the apex beat was in the anterior axillary line in the fifth intercostal space. There was a systolic thrill and murmur and also an early diastolic murmur in the second left intercostal space. There was marked pulsation in a prominent right common carotid artery. His blood pressure was 90/40. On radioscopy both ventricles appeared to be enlarged and the main pulmonary artery and its branches were increased in size and pulsation, and the aortic arch was high. The cardiogram appeared to show enlargement of both ventricles (T in aVL inverted, R in V5 plus S in V2 equals 50 mm., R in V4R equals 15 mm.). At cardiac catheterization the pressures in mm. Hg were: right atrium (R.A.) 4/1, right ventricle

(R.V.) 108/0, pulmonary artery (P.A.) 103/58, aorta 120/70. Oxygen saturations were R.A. 68, R.V. 68, P.A. 79, and aorta 88 per cent. A left lateral angiogram showed a greatly enlarged innominate artery.

At thoracotomy at the age of fourteen, there was an aneurysmal dilatation of the arch of the aorta and the pulmonary artery was also very large. There was a very large patent ductus which was ligated. The P.A. pressure was 88/55 before and 48/25 mm. after ligation. Two weeks later his blood pressure was 100/70 and there was a loud systolic murmur all over the præcordium maximal in the suprasternal notch and an early diastolic murmur down the left sternal edge. A phonocardiogram showed a diamond-shaped



A B

FIG. 2.—*Case* 4. (A) High frequency phonocardiograms before operation showing (from above downwards) a continuous murmur in the first left intercostal space, a systolic murmur of diamond shape, and an early diastolic murmur in the third left intercostal space, and a mid-diastolic murmur at the apex. (B) Phonocardiograms after operation. The upper three channels in the second right intercostal space (from above downwards: low, medium, and high frequencies) show a persistent diamond-shaped systolic murmur and an early diastolic murmur. The lower three channels in the second left intercostal space (from above downwards: low, medium, and high frequencies) show the disappearance of the continuous murmur.

systolic murmur at the base and apex and an early diastolic murmur at the base. A year later a chest X-ray showed that the pulmonary artery and its branches were considerably smaller; the electrocardiogram had changed slightly, T in aVL now being isoelectric.

Summary. Patent ductus arteriosus, aortic stenosis and incompetence.

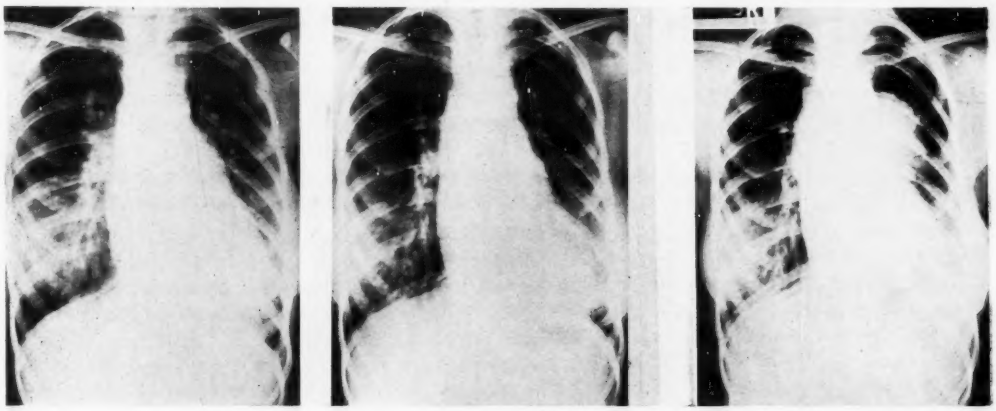
Case 6. A.A. (female). She was found to have a cardiac murmur when 10 days old. At the age of 9 years, she had subacute bacterial endocarditis (blood culture grew *Streptococcus viridans*) and after treatment with penicillin made an apparent complete recovery. When first seen at St. Thomas' Hospital a year later, she had slight dyspnœa on exertion. She was small for her age and thin. Her blood pressure was 130/0. There was unusually vigorous pulsation in the carotid, axillary, brachial, and retinal arteries and there was a pistol shot over all the peripheral arteries down to the radial and dorsalis pedis. There was a systolic and diastolic thrill and murmur maximal in the third left intercostal space. The murmurs appeared to be to-and-fro rather than continuous. X-rays showed left ventricular enlargement, a prominent first

part of the aorta and a marked aortic fling. The main pulmonary artery was enlarged but its branches were normal. The cardiogram was normal. A phonocardiogram showed a systolic murmur maximal in mid systole in the second left intercostal space. There was no murmur at the second sound, which was followed by an early diastolic murmur. At cardiac catheterization the oxygen saturations were R.V. 66 and P.A. 76 per cent, and this suggested a patent ductus, although the clinical picture was dominated by severe aortic incompetence.

At thoracotomy a small patent ductus was ligated and the thrill previously palpable in the main pulmonary artery became less intense. Examination after operation showed no change in the signs. Two years later she was examined by Dr. Maurice Campbell and Dr. Paul Wood at the National Heart Hospital and they have kindly provided the results of a further catheterization: pressures, R.V. 57/0, P.A. 37/17 (indicating mild pulmonary stenosis); and oxygen saturations, P.A. and R.V. 76, R.A. 61, and brachial artery 94 per cent. This shunt was thought to indicate a ventricular septal defect but in view of the previous subacute bacterial endocarditis rupture of an aortic sinus into the right ventricle was a remote alternative. At the age of sixteen we found that the physical signs of gross aortic incompetence remained, her blood pressure being 220/0 mm. The systolic thrill was still present in the fourth left intercostal space and may be caused by the ventricular septal defect. A cardiogram showed early left ventricular hypertrophy.

Summary. Patent ductus arteriosus, aortic incompetence, mild pulmonary stenosis, and probable ventricular septal defect. (Case E3, Table IX, Campbell, 1954).

Case 7. D.C. (female). At the age of seven she was found to have an abnormal heart. She was first seen at St. Thomas' Hospital at the age of fifteen and was then symptomless apart from slight dyspnœa on exertion. Her fingers showed arachnodactyly and she had a coloboma of the left iris. There was a lifting apex beat in the sixth intercostal space in the anterior axillary line. There was a continuous thrill maximal in the second left intercostal space with an extremely loud continuous murmur. To the right of the sternum there was an early diastolic murmur higher in pitch than the diastolic element of the continuous murmur. Her blood pressure was 115/35. X-rays (Fig. 3A) showed apparent enlargement of both ventricles, prominence of the first part and arch of the aorta, and enlargement of the main pulmonary artery and its



A B C

FIG. 3.—*Case* 7. (A) Before operation. (B) Four months, and (C) nine months after operation, showing decrease in heart size and pulmonary vascular markings in (B) and the aneurysmal dilatation of the pulmonary artery which later develped in (C).

branches. The cardiogram showed gross left ventricular strain. At cardiac catheterization the pressures in mm. Hg were: R.A. mean 1, R.V. 58/0, and P.A. 52/28, and the oxygen saturations were superior vena cava 56, inferior vena cava, 62, R.A. 57, R.V. 59, and left P.A. 80 per cent.

At thoracotomy a large patent ductus was found and ligated. There was slight dilatation of the aorta at its junction with the ductus and this became more marked after the ligation. After operation her blood pressure was 140/75 and there was a to-and-fro murmur to the right of the sternum but the continuous

murmur to the left of the sternum had gone. Two months later a quiet continuous murmur had returned and this was confirmed by phonocardiography (Dr. Leatham). However, the pulmonary artery and its branches were considerably smaller (Fig. 3B) and at cardiac catheterization the colour of the right ventricular and pulmonary arterial samples looked the same (due to a technical error they were not analysed), so it was concluded that the ductus had recanalized but that the shunt was only small. Nine months after operation she was found on routine chest X-ray to have developed an extreme aneurysmal dilatation of the pulmonary artery (Fig. 3C). Seventeen months after operation she felt very well and had started shorthand and typing. The signs of aortic incompetence and the X-ray appearances remained the same but the continuous murmur had disappeared.

Summary. Patent ductus arteriosus, aortic incompetence, possible recanalization of the ductus, development of aneurysm of pulmonary artery.

Case 8. R.R. (male). He was first seen at St. Thomas' Hospital when aged five. He was symptomless but a murmur had been heard by his doctor. His mother said that her sister, who lived with her, had had rubella when she, his mother, was two months pregnant. He had been born with a cataract in his right eye and despite an operation could count fingers only with this eye, and the visual acuity in his left eye was 6/36; this was found by an ophthalmologist to be due to pigmentary degeneration at the macula. He was small for his age. There was a loud systolic murmur maximal in the pulmonary area but no diastolic murmur. A year later a diastolic murmur was heard and at the age of seven there was a continuous murmur in the second left intercostal space. It was noted that the systolic element of the murmur radiated both to the neck and to the back. At thoracotomy a ductus was found but there was also a coarctation of the aorta and because of that finding the ductus was not then ligated. On re-examination afterwards no circulatory abnormalities due to the coarctation were found; the femoral and radial pulses were synchronous and the blood pressure in the legs 115/65. At the age of ten cardiac catheterization showed: (pressures in mm. Hg) R.A. mean 0, R.V. 15/3, P.A. mean 13; and oxygen saturations, R.A. 60, R.V. 60, and P.A. 85 per cent. In view of the size of the shunt the ductus was ligated at a second operation. After operation there was a thrill and harsh systolic murmur at the base, equal both sides of the sternum but radiating up into the neck. There was no diastolic murmur. The cardiogram showed incomplete right bundle branch block.

Summary. Patent ductus arteriosus, aortic stenosis, and mild coarctation of the aorta.

Discussion

All these patients were diagnosed before operation as having a patent ductus arteriosus (P.D.A.) either on the basis of the passage of a catheter through it or because of a shunt of arterialized blood into the pulmonary artery.

The frequency of associated anomalies and the presence of local signs suggesting aortic valve disease were the two chief features that distinguished them from uncomplicated cases of P.D.A.

Associated Anomalies. These will be considered under two headings, extracardiac and cardiac. The extracardiac anomalies were as follows. Four cases had congenital eye defects, stippled retinæ (Case 3), bilateral cataracts (Case 5), coloboma of the left iris (Case 7), and cataract in the right eye and pigmentary degeneration of the left macula (Case 8). Two of these (Cases 3 and 7) also had arachnodactyly and one (Case 5) had bilateral congenital deafness. Two of these (Cases 3 and 5) had a history of maternal rubella in the relevant pregnancy, and in one (Case 8) his mother was in contact with rubella while two months pregnant, but in the others pregnancy and delivery were normal. Four (Cases 2, 5, 6, and 8) were under weight.

The associated cardiovascular anomalies were as follows. Mild coarctation of the aorta was seen in one (Case 8): this was an operative finding and was not severe enough to produce arm hypertension, collateral vessels, or diminution or delay in the femoral pulses. One (Case 5) had a greatly enlarged innominate artery. In one (Case 6) cardiac catheterization two years after her P.D.A. had been ligated showed mild pulmonary stenosis and a probable ventricular septal defect. One (Case 7) developed an aneurysmal dilatation of the pulmonary artery after operation. Case 2 had a double superior vena cava.

Signs suggesting Aortic Valve Disease. These can be divided into signs produced at the abnormal valve itself and signs indicating increased left ventricular work.

In three of the four patients with a continuous murmur to the left of the sternum an aortic

valve lesion was suspected before operation on the basis of a systolic thrill maximal to the right of the sternum (Case 4), phonocardiographic evidence that the systolic murmur was maximal in mid systole (Case 3), and a diastolic murmur to the right of the sternum differing in pitch from the diastolic element of the continuous murmur (Case 7). Of the four patients without a continuous murmur three also were suspected of having an aortic valve lesion preoperatively because two (Cases 1 and 2) had a systolic thrill conducted up into the neck, and the other (Case 6) had a very high pulse pressure and pistol shot sounds over the peripheral arteries suggesting aortic incompetence. In Cases 5 and 8, an aortic valve lesion was not diagnosed until after the abolition of the murmurs of the P.D.A.

The signs indicating increased left ventricular work were: cardiac enlargement with a left ventricular type of apex beat (7 cases) and left ventricular hypertrophy both on screening (7 cases) and in the electrocardiogram (5 cases). In the absence of aortic incompetence, if a case of P.D.A. has a comparatively small pulse pressure (indicating a moderate or small shunt) the presence of left ventricular hypertrophy suggests aortic stenosis.

Post Operative Course. Cases 1–4 were operated upon by Mr. D. J. Waterston at Great Ormond Street Hospital for Sick Children, and Cases 5–8 by Mr. N. R. Barrett at St. Thomas' Hospital.

In six patients the P.D.A. was large and in two (Cases 1 and 3) of these, the cardiothoracic ratio dropped from 75 and 70 to 59 and 55 per cent respectively after operation. In five of these patients the pulmonary vessels became much smaller after operation but in the remaining one (Case 7) after an initial decrease there developed the aneurysmal dilatation of the pulmonary artery previously described. In the two patients with a small P.D.A. (Cases 6 and 8) the X-ray appearances after operation were unchanged. In no case did the cardiographic changes of left ventricular hypertrophy return to normal after operation.

Aortic valvotomy has not been attempted in any of these patients, but in those with aortic stenosis in whom a large left ventricular load persists after ligation of the P.D.A. it might be considered in the future.

Summary

Eight patients with a patent ductus arteriosus and an aortic valve lesion are presented and the reported cases are briefly reviewed.

An aortic valve lesion may be suggested either by murmurs and thrills recognizably separate from those of the patent ductus or by evidence of left ventricular hypertrophy out of proportion to the size of the shunt.

Associated cardiovascular and other anomalies were common in these cases. In two or perhaps in three the mother had suffered from rubella in the second month of her pregnancy.

We are grateful to Mr. D. J. Waterston and Mr. N. R. Barrett for their co-operation, to Dr. Maurice Campbell and Dr. Paul Wood for supplying the results of cardiac catheterization at the National Heart Hospital in Case 6, to Dr. B. Weeks, Dr. Aubrey Leatham, and Dr. E. D. H. Cowen for the phonocardiograms in Cases 4, 7, and 6 respectively, and to Messrs. D. Martin and K. G. Moreman for the photographs.

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BASIL T. PARSONS-SMITH

Basil Thomas Parsons-Smith, Consulting Physician to the National Heart Hospital, died after a short illness at his home in Tadworth, Surrey, on September 3, 1954, at the age of 72.

He received his early education at Sir Roger Manword's Grammar School, Sandwich, and his medical training at St. Thomas's Hospital where he qualified in 1907 and, after holding the posts of casualty officer and house physician, obtained the M.D. (Lond.) in 1909. He served in France during the first World War, and for a time was in charge of the heart centre at Cayeux-sur-Mer. On demobilization he obtained the M.R.C.P. (Lond.), and became heart specialist to the Ministry of Pensions, and Assistant Physician to the Cardiac Department at St. Thomas's Hospital. He was elected F.R.C.P. (Lond.) in 1929.

He was appointed Physician to Outpatients at the National Heart Hospital in 1920 and became Physician to the Hospital in 1929, a position that he held for 18 years. He acted as Dean to its Postgraduate Medical School from 1923 until 1947 and helped in the arrangements for the new Institute of Cardiology. On his retirement from the staff in October 1947 he was elected a member of the Committee of Management of the Hospital and in July, 1948, became a member of the Board of Governors, the meetings of which he attended regularly up to July, 1954.

In 1914 he was awarded the Hunterian Medal for a dissertation on the intermittent pulse. He delivered the Hunterian Society Oration in 1934, the St. Cyres Lecture at the National Heart Hospital in 1936, and the Lumleian Lectures dealing with the subject of heart failure at the Royal College of Physicians in 1950. He was president of the Clinical Section of the Royal Society of Medicine from 1936 to 1938, and of the Hunterian Society in 1952 when his inaugural address dealt with the progress of cardiology. He was a founder member of the British Cardiac Society and of the London Cardiological Club, serving as secretary of the latter from the start in 1922 till 1950.

He was an ardent Freemason and held office in Grand Lodge. He liked a game of golf and excelled at cricket, playing for St. Thomas's XI when an undergraduate, and on the village greens of Winchelsea and Buxted between the two world wars. He was a keen gardener and his lawns like himself grew no tares. He found no fault in others for he was without guile himself. Basil Parsons-Smith walked gracefully through life, erect in posture and likewise in character. No one could have been kinder to his friends and to his patients who received from him, in addition to skilled medical care, that sympathetic understanding which gave them strength to endure their suffering the more easily in that he shared it with them. Indeed, he was a good doctor and loved his calling so that he continued in active consulting practice after his retirement from hospital work.

He will be missed sorely by his friends and how much more at his home, where he both gave and received such great happiness; in 1910 he had married Marguerite, the daughter of Sir David Burnett, former Lord Mayor of London, and it is to her in her great grief, to their son who follows him in the profession, and to their daughter, that we extend our deep sympathy in their irreparable loss.

WILLIAM EVANS

BASIL T. PARSONS-SMITH

CASE REPORTS

GIANT CELL ARTERITIS WITH ANEURYSMAL FORMATION IN AN INFANT

BY

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From Salisbury Native Hospital, S. Rhodesia

As an aneurysm is rare in infancy or childhood, it is considered of interest to publish the following details of a case in which it appeared macroscopically to be syphilitic, but histologically proved similar to the condition described as " giant cell arteritis."

Case Report

The patient was a male (Mashona) African aged about two years. He was carried into hospital on October 16, 1950, by his mother who stated that ten days previously he had begun to experience difficulty in breathing. He had become progressively worse, alarmingly so on the day that his mother sought help at the hospital.

On examination the patient was a well nourished, healthy looking male infant who was struggling for breath and finding expiration more difficult. The temperature was 98° F. and the pulse rate 130 a minute. The lips and tongue were intensely cyanosed and the eyes congested with a serous discharge issuing from both. No obvious obstruction could be seen on inspection of the glottis and pharynx. The neck veins were distended and the head thrown back but no cervical lymphadenopathy was noted.

Respiration was grunting in type and this made examination of the chest difficult. No adventitious sounds were detected and dullness was not apparent. The apex beat was palpable 1 cm. beyond the left nipple line. The heart rate was 130 a minute and the sinus rhythm was interrupted by short periods of irregularity. The liver edge was barely palpable and the spleen could not be felt. The child was semi-conscious but no abnormality in the central nervous system was detected. A radiograph of the chest revealed the presence of a large mass in the superior mediastinum which extended into the lung fields on both sides, but more prominently into the right upper zone. The rest of the lung fields were clear (Fig. 1). The " tumour " was considered to be a thymoma.

The patient died a few hours after admission.

Necropsy Report

The subject was a healthy looking child of about two years with thin arms and legs. The brain showed moderate congestion of vessels. The tonsils were enlarged and inflamed and the lungs broncho-pneumonic. A slight hilar adenitis was present. Both ventricles of the heart were moderately dilated, the right ventricle showing a moderate degree of hypertrophy. All the valves were normal. The aorta was normal for the first 6 cm., after which it showed a fusiform dilatation for about 15 cm. of its length associated with well-marked longitudinal puckering of the intima and thickening. There was no evidence of atheroma macroscopically, but there was a superficial patchy ulceration. The abdominal aorta had the same scarring extending to just below the origin of the superior mesenteric artery. The right subclavian artery was dilated and contained an organizing thrombus. The aneurysm measured $3{\cdot}3 \times 2{\cdot}5$ cm. All other vessels appeared normal. The liver was congested and the spleen moderately large. Mesenteric adenitis was conspicuous. All other organs were within normal limits.

Histology. The *intima* of the aorta was thickened owing to the laying down of fine collagen fibres and a fibroblastic proliferation. The internal elastic lamina was completely destroyed in parts. There was a moderate plasma cell and lymphocytic infiltration but no thrombus. The media showed almost complete destruction

FIG. 1.—X-ray of chest showing density in superior mediastinum, mainly on the right, due to fusiform aneurysm of ascending and descending aorta and right subclavian artery.

of the entire elastic tissue with a fibroblastic proliferation and its replacement by collagen fibres. There was a patchy infiltration of the media by polymorphonuclear leucocytes, plasma cells and lymphocytes which, in some parts, were associated with variously shaped and sized giant cells. Some of these had their nuclei placed circumferentially while in others the nuclei were aggregated together. There was no sign of caseation or necrosis. The inflammatory reaction was mainly in the central part of the media. The *adventitia* showed fibrosis. The process was a gradually developing one when sections of normal to abnormal aorta were examined, the earliest change appearing to be a leucocytic infiltration of the intima and media. Sections of the subclavian aneurysm were identical histologically.

The anterior descending branch of the left coronary artery showed intimal thickening (localized and irregular) due to the laying down of fine collagen fibres with destruction of the internal elastic lamina but with little evidence of inflammation. The lungs were affected with a non-tuberculous broncho-pneumonia. The myocardium revealed no evidence of Aschoffs' nodules. The liver showed a severe passive venous congestion with no evidence of congenital syphilis. The kidneys appeared to be within normal limits.

No spirochætes or tubercle bacilli were discovered in sections, and smears from the lungs showed no tubercle bacilli.

Cause of death. Asphyxiation due to aneurysm of the aorta and of the right subclavian artery with bronchopneumonia.

Discussion

Calvin and Nichamin (1934) list the causes of aortic aneurysms in children as follows: (i) atheromatous degeneration; (ii) trauma; (iii) erosion of aorta from without; (iv) congenital malformation; and (v) acute infectious diseases—especially rheumatic fever.

Aneurysms in children have been described in the left renal artery by Howard *et al.* (1940) in a child of five years suffering from essential hypertension; of the pulmonary artery in a girl, aged twelve years, by Hartwell and Tilder (1943) and in the thoracic aorta in a boy of four and a half years, by Bronson and Sutherland (1928). Calvin and Nichamin (1934) found an aortic aneurysm in two patients with lesions which, prior to death, were regarded as rheumatic; the first was in

an eleven-year-old child with coarctation of the aorta and the second in a child of four years with an aneurysm of the abdominal aorta in whom no evidence of arteriosclerosis or specific pathology was found.

The ætiology of the arteritis and aneurysm in our patient appears to be different from the causes just quoted. There was no evidence histologically of atheroma, syphilis, rheumatic fever or tuberculosis, which were features of previously reported cases. The histological changes found in the present case appear to conform to those usual in " giant cell arteritis." Gilmour (1941) introduced this term to denote a condition that is similar histologically to " temporal arteritis." Giant-cell arteritis may affect many arteries in a wide-spread manner. In an affected vessel there is intimal thickening without thrombus owing to an increase in cellular fibrous tissue and infiltration with macrophages and lymphocytes and to a lesser degree with plasma cells. The line of demarcation from the media is indistinct, large segments of the internal elastic lamina being destroyed. The maximal lesion is seen in the media. Of interest, too, are the areas of coagulative necrosis and a heavy cellular infiltration similar to that found in the intima. Multinucleated giant cells of both the foreign body and Langhans types are characteristically present. The adventitia shows a cellular infiltration similar to that of the media but to a lesser extent, and without giant cells. In most cases a varying degree of atheroma is also present in the artery. Aneurysm formation, too, has been described in giant cell arteritis. McMillan (1950) has reported two cases of aneurysm formation of the aorta and Gilmour (1941) recorded a death from rupture of an aneurysm of an affected subclavian artery.

Giant-cell arteritis usually occurs in adults over the age of 40. In nearly all instances so far reported symptoms suggesting an infection had been observed some weeks or months before manifestations of the arteritis developed. The disease may be self-limited, healing after a few weeks or months. In fatal cases, however, death is either from the indirect effects of the arteritis or from independent causes.

The case reported in the present paper differs from the above mainly on the grounds of age and the absence of atheroma.

Summary

An account is given of the clinical, post-mortem, and histological features of giant-cell arteritis in an African male infant, aged two years. The disease produced a fusiform aneurysm of the right subclavian artery with dilatation of the ascending and descending aorta. No evidence of syphilis, tuberculosis, rheumatic fever, or atheroma was discovered.

I wish to thank Dr. G. Blaine for the pathological and histological reports on the case, and Dr. R. M. Morris, O.B.E., for his permission to publish this paper.

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TRANSITORY W-P-W ABERRATION AFTER INTRAVENOUS STROPHANTHIN

BY

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In view of certain unusual electrocardiographic features, the following case is considered worth reporting.

Case Report

A 68-year-old Hindoo male, who had been under treatment for years for hypertension, was seen in a state of left ventricular failure in February, 1953. On examination, he was found to be orthopnœic and pale, with a markedly displaced and heaving apex beat and a loud systolic murmur over the præcordium. The blood pressure was 176/112 mm. His electrocardiogram (Fig. 1), showed left ventricular strain with digitalis defect.

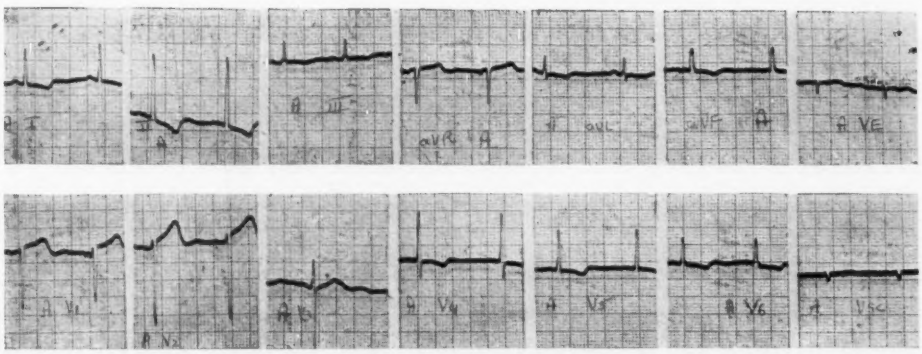

FIG. 1.—Electrocardiogram, taken on 13/3/53, showing a left ventricular strain pattern, with pathological P waves, normal P–R and QRS duration and pathological S–T–T segments. Above: standard leads, unipolar limb leads and VE. Below: chest leads V1 to V6 and VCL.

On 14/3/53, within half an hour of an intravenous injection of 0·25 mg. of k-strophanthin or kombetin, he complained of palpitation. Fig. 2 taken at this time showed, in addition to the normal complexes of the patient, numerous complexes (marked W) with ventricular aberration of W-P-W type with " pre-excitation," mostly in groups of two, three or four, alternating with similar groups of normally conducted beats (cf. lead V6 of Fig. 3). Besides this, there were long strips of continuous W-P-W aberration (lead II of Fig. 3), long strips of normally conducted beats (leads V2 of Fig. 3) and regular alternation of normal and W-P-W beats (lead V6 of Fig. 3).

Several electrocardiograms taken during the next few days showed a return of the pattern to normal with no aberrant complexes, whatsoever.

Discussion

The W-P-W syndrome (Wolff, Parkinson, and White, 1930) has been reported in association with hypertension and hypertensive heart disease (Lepeschkin, 1951), as well as after the administration of digitalis

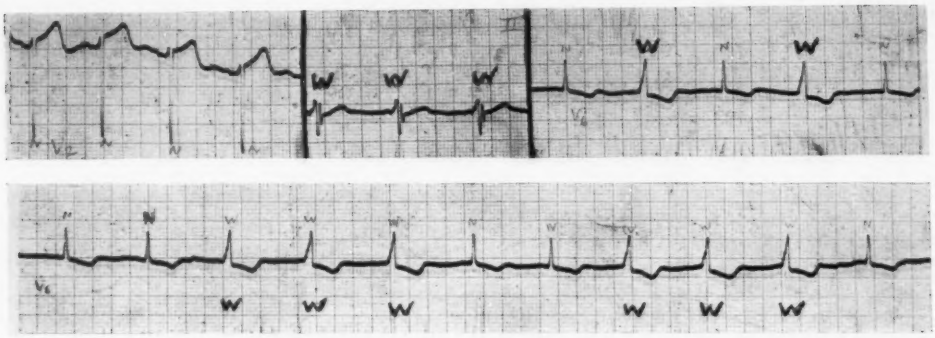

FIG. 2.—Electrocardiogram, taken on 14/3/53, showing aberrant complexes with pre-excitation. P–R=0·06 sec., QRS complexes, wide and slurred or notched. Above: leads V2, II, and V4: below; V1.

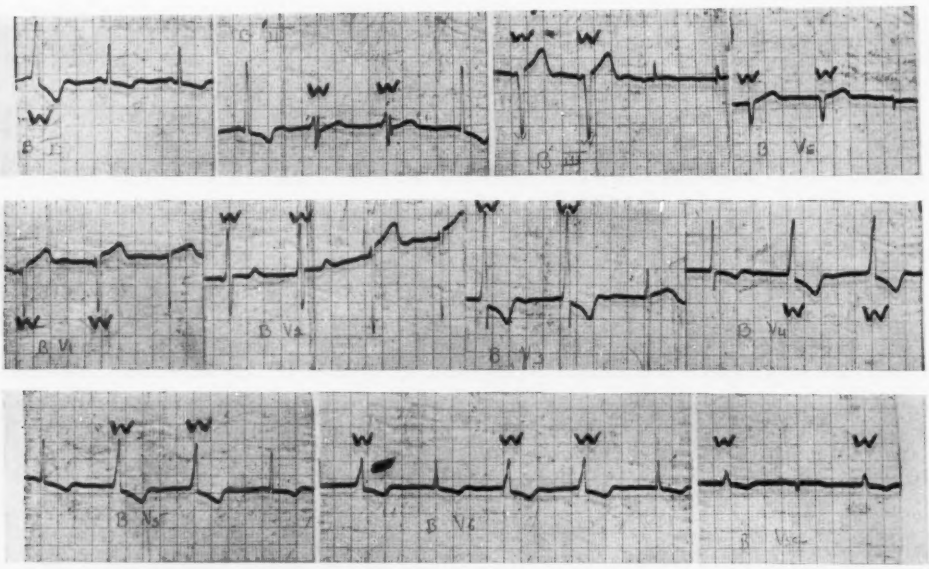

FIG. 3.—Selected strips, from the electrocardiogram of 14/3/53, showing in lead V2 a continuous stretch of normally conducted beats; in lead II, a stretch of W-P-W beats; in lead V6, regular alternation of beats; in lead V6 (lower strip), alternation of grouped beats. Upper row: standard leads and VE. Lower rows: chest leads V1 to V6 and VCL.

and allied preparations (Öhnell, 1944; Lepeschkin, 1951; and Prinzmetal *et al.*, 1952). In animals, W-P-W aberration has been reported after toxic doses of strophanthin and ouabain (Lindner, 1944; Prinzmetal *et al.*, 1952).

The present case is interesting in that it reports the transitory development of W-P-W aberration after a single non-toxic dose of k-strophanthin in an elderly subject of hypertensive heart disease. A close study of the aberrant complexes in the various leads reveals a varying degree of ventricular aberration. Another feature of interest is the unusual degree of prematurity of the initial component of the aberrant ventricular complex, which seems to arise actually during the inscription of the P wave (cf. leads I and II of Fig. 2 and lead II of Fig. 3).

In view of the close resemblance of the aberrant ventricular complexes (cf. leads II, III, V2, V3, VE, and Vcl) to ventricular extrasystolic beats, the transitory nature of the aberration, the age of the patient, and absence of a history of paroxysmal tachycradia, I am inclined to attribute the W-P-W aberration in this case to an irritable focus in the ventricular musculature.

The unusually premature excitation of the ventricle suggests the possibility of activation of the ventricular focus by the electrical or mechanical effects of auricular activity (Lepeschkin, 1951).

Summary

Transitory aberration of W-P-W type is described after an intravenous injection of a single non-toxic dose of k-strophanthin in an elderly hypertensive with left ventricular failure. This is probably the first case of its kind reported.

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Lindner; cited by Öhnell (1944).

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ABSTRACTS OF CARDIOLOGY

Edited in collaboration with Abstracts of World Medicine

A Clinical Appraisal of Pentapyrrolidinium (M & B 2050) in Hypertensive Patients. E. D. FREIS, E. A. PARTENOPE, L. S. LILIENFIELD, and J. C. ROSE. *Circulation* (*N.Y.*), **9**, 540–546, April, 1954.

The authors report the results of a comparative study of the effect of a new ganglionic blocking agent, pentamethylene 1:5-bis-(1-methylpyrrolidinium) bitartrate (pentapyrrolidinium, "M and B 2050") and hexamethonium chloride on the blood pressure of hypertensive patients. In 27 patients with severe fixed hypertension treated during 2 to 6 months solely with pentapyrrolidinium given orally in three doses a day, the mean total daily effective dose was 300 mg. (range 135 to 630 mg.). In these patients the average blood pressure fell from 230/135 mm. Hg (range 180/110 mm. to 260/160 mm. Hg) before treatment to 170/110 mm. (range 130/95 to 210/130 mm. Hg) after treatment.

Cross tolerance between the two drugs was very small, and tolerance developed to pentapyrrolidinium less often than to hexamethonium. The side-effects of the drug were similar to those of hexamethonium, impotence being particularly frequent and troublesome. One important advantage of pentapyrrolidinium was that its onset of action was far more predictable than that of hexamethonium and, in contrast to the latter, oral administration lowered the blood pressure significantly without producing prolonged collapse or paralytic ileus. It is emphasized, however, that critical adjustment of the dose is necessary, which is a definite drawback, since a slight excess may produce hypotensive reactions such as postural faintness, and slight underdosage may fail to lower the blood pressure significantly. The authors therefore recommend that its use be confined to cases of severe hypertension which have not been benefited by simpler measures.

A. Schott

Arterial Hypertension Treated with *Rauwolfia serpentina* and *Veratrum viride*. C. JOINER and R. KAUNTZE. *Lancet*, **1**, 1097–1099, May 29, 1954.

A clinical trial was conducted in which hypertensive patients taking veratrum viride in the form of "veriloid" were also given rauwolfia serpentina. This treatment was suggested by reports that rauwolfia possessed additive properties in lowering the blood pressure when given with other hypotensive drugs. A total of 24 patients were selected for the trial, but 8 had to be withdrawn before the end; thus the results in 16 cases only are present. All the patients received veriloid, 1 mg. per 10 lb. (4·5 kg.) body weight, throughout the 16 weeks of the trial. Rauwolfia was given in addition to the veriloid—to 10 patients in a nightly dose of 0·5 g. for the second 8 weeks of the study, and to 6 patients in a nightly dose of 0·5 g. for the first 8 weeks and of 1 g. for the remaining 8 weeks.

The addition of rauwolfia serpentina resulted in a bradycardia in 6 patients; in 6 others there was a fall in diastolic pressure, which was, however, clinically significant only in 3 (a fall of 14 to 45 mm. Hg). Increasing the dose of rauwolfia from 0·5 to 1 g. had no effect in the 6 cases in which this was done. No serious toxic effects were observed, but in 2 patients pruritus with urticaria developed.

The authors conclude that in the dosages used there is no clear evidence of an additive effect of the two drugs.

Arthur Willcox

The Uncommon Heart Diseases. NATHANIEL E. REICH, M.D. Oxford: Blackwells Scientific Publications, 1954. Pp. 516, Figs. 110. 75*s*.

This book is intended as a supplement to the standard textbooks on heart disease. A large amount of the material included would seem to have no place in a book with this title, as for example the effects of pregnancy, obesity, anæsthesia, or aortic insufficiency on the cardiovascular system, whereas many of the more uncommon types of heart disease are more adequately covered in several of the larger standard works available. The value of this book for reference purposes is limited by the fact that the bibliography is confined almost entirely to the American literature. *G. W. Hayward*

A Primer of Congestive Heart Failure. GEORGE E. BURCH. Oxford: Blackwells Scientific Publications, 1954. Pp. 126. 30*s*.

This monograph, one of the American Lecture Series, summarizes present ideas on the mechanism of congestive heart failure and discusses the difficulties in accepting many of the clinical concepts. The chapter on treatment is written from an essentially practical point of view and the chapters on digitalis and the mercurial diuretics describe clearly the mode of action and method of administration of these drugs. This book which was primarily intended for the young graduate in medicine and the general practitioner can be recommended to all physicians interested in the problem of congestive heart failure. *G. W. Hayward*

Painless Myocardial Infarction: a Review of the Literature and Analysis of 220 Cases. M. D. ROSEMAN. *Ann. intern. Med.*, **41**, 1–8, July, 1954.

In 10 out of 220 cases of myocardial infarction proved by necropsy or serial electrocardiography at the Boston City

Hospital, the patient complained of no pain or discomfort. Only in 5 of the 10 was it possible to obtain a reliable history. Of these, 2 patients had a long history of angina but had no pain at the time of the infarction, and it is considered that in these cases slow and progressive narrowing of the coronary vessels may have resulted in relative anæsthesia of the infarcted area from destruction of the vessels and nerves, so that the final occlusion caused no pain. The other patients may have been hyposensitive individuals in whom the marked dyspnœa which accompanied the attack overshadowed a moderate amount of pain. From this series and a survey of the literature it is concluded that painless myocardial infarction is rare. *C. W. C. Bain*

Endomyocardial Fibrosis in Africa: Its Diagnosis, Distribution and Nature. A. W. WILLIAMS, J. D. BALL, and J. N. P. DAVIES. *Trans. roy. Soc. trop. Med. Hyg.*, **48**, 290–311, July, 1954.

From their experience at Mulago Hospital (Makerere College Medical School), Kampala, Uganda, the authors consider endomyocardial fibrosis to be one of the commonest causes of death from heart failure among Africans in this area. Analysis of a seris of 231 necropsies on patients dying of heart failure showed that the four main causes were endomyocardial fibrosis, 33 cases (14%); renal hypertension, 37 (16%); syphilitic aortitis, 34 (15%); and rheumatic heart disease, 20 (9%). They do not consider it likely that the disease is peculiar to this small area of Africa, but attribute the comparatively high incidence here reported to the rise in the number of necropsies performed and the increased awareness of the condition at Kampala. Only fragmentary information is available on the incidence of endomyocardial fibrosis elsewhere; most of this is from Africa, but a few cases have been reported from the United States and from Europe.

Since in most cases only the end-results of endomyocardial fibrosis are seen, the nature of the onset and development of the condition are unknown. Post mortem, the left ventricle shows endo- and myo-cardial fibrosis and the posterior cusp of the mitral valve may be adherent to the ventricle wall. The right ventricular lesion usually produces obliteration of the cavity in the region of the apex, and ocasionally the the posterior cusp of the tricuspid valve becomes adherent to the ventricle. Clinically, these pathological changes result in left, right, or bilateral heart failure, with or without mitral incompetence or tricuspid incompetence. X-ray screening shows a large, globular heart shadow and greatly decreased pulsation, which is presumably due to poor myocardial contractility. Low-voltage electrocardiograms are common, but arrhythmia is rare.

The pathogenesis is largely speculative; two possible sequences are discussed, namely, endocardial damage leading to thrombosis followed by fibrosis, or subendocardial muscle injury resulting in endocardial thrombosis and again fibrosis. The roles of infection, allergy, malnutrition, and toxic agents as possible ætiological factors are considered. Of infection, the authors state that " the possibility of virus infection (by itself or with some other contributing factor) initiating a fibrosis–thrombosis or thrombosis–fibrosis cycle involving the inner layers of the heart wall cannot be dismissed," In conclusion a plea is made for further information about the geographical and racial distribution of this condition, and the difficulties involved in studying the lesion in its early stages are emphasized. *J. Warwick Buckler*

Endomyocardial Fibroelastosis. A Study of Thirty Cases. W. R. HALLIDAY. *Dis. Chest.*, **26**, 27–40, July, 1954.

" Endomyocardial fibroelastosis " is regarded by the author as the most descriptive of the many names which have been applied to a condition of which the essential pathology consists in " a diffuse or focal thickening of the endocardium and subendocardial myocardium, consisting predominently of fibrous and elastic tissue." He was able to collect 30 cases (18 male, 12 female) from the post-mortem records of the Children's Hospital, Denver, Colorado, over a period of 5 years. The age at death varied between a few hours and 20 years and it is suggested that occasional patients may survive even longer.

The left side of the heart was more frequently and more severely involved than the right. In 17 cases the disease was associated with a great variety of congenital cardiovascular defects (which were the cause of death in 16) including coarctation of the aorta in 7 cases, patent foramen ovale in 8, patent ductus arteriosus in 9, and infundibular stenosis in 2. Anomalies of the coronary arteries were present in 5 cases, but these could not have produced myocardial ischæmia. In 11 cases (including 2 of these 17) various non-cardiovascular abnormalities were present, which were fatal in 4 cases. The remaining 10 patients died of endomyocardial fibroelastosis. In several cases hypoplasia of one or more chambers of the heart was present, but it could not be determined whether this was a result of the disease or of the associated abnormalities. *F. Starer*

Pressures in the Left Auricle and Ventricle in Mitral Stenosis before and after Commissurotomy. B. I. LATSCHA, F. DE'ALLAINES, and J. LENÈGRE. *Arch. Mal. Cœur.*, **47**, 385–409, May, 1954.

The pressures within the left auricle, left ventricle, and aorta were measured with an electromanometer by direct needle puncture after the pericardium had been opened at operation in 70 patients with mitral stenosis undergoing mitral commissurotomy.

In pure mitral stenosis the left auricular pressure was roughly halved as a result of operation on the valve, the pressure being usually in the region of 30 mm. Hg before operation. The left ventricular systolic pressure was found to be low initially in pure mitral stenosis, the average being 78 mm. Hg, and rose after satisfactory valvotomy to an average of 115 mm. Hg. Except when the mitral stenosis was accompanied by aortic regurgitation, the left ventricular diastolic pressure was normal initially and was unchanged after operation. When mitral incompetence was predominant, the left ventricular pressure was often raised.

The authors made the surprising observation, by simultaneous recording of the pressures within the left ventricle and aorta, that the systolic pressure in severe

mitral stenosis may be higher in the aorta than in the left ventricle, this difference being reduced by valvotomy.

G. S. Crockett

The Electrocardiographic Effects of Intravenous Administration of Neostigmine and Atropine during Cyclopropane Anesthesia. E. JACOBSON and M. H. ADELMAN. *Anesthesiology*, **15**, 407–415, July, 1954.

Several reports have appeared of the occurrence of sudden death following the intravenous administration of neostigmine and atropine in anæsthetized and curarized patients. The present authors, in an attempt to explain the cause of these sudden deaths, have closely followed the sequence of events in 20 patients who were premedicated with morphine and atropine and anæsthetized with cyclopropane, electrocardiographic records being taken continuously before and during anæsthesia. Atropine was given to each patient at the height of neostigmine activity. The changes following the intravenous injection of neostigmine were: little change in blood pressure, the development of sinus bradycardia, first degree auriculo–ventricular block, increased amplitude of the QRS complex, and increased prominence of the T wave. There was no evidence to support the theory of Bain and Broadbent (*Brit. med. J.*, 1949, **1**, 1137) that atropine potentiated the cholinergic effects of neostigmine by central vagal stimulation. On the contrary, in every case here studied, intravenous atropine produced opposite effects; these were heralded by reactivation of sinus activity and followed by increased auriculo–ventricular conduction.

The authors speculate on the cause of death due to neostigmine. This substance alone, in a normal patient under cyclopropane anæsthesia, can produce profound disruption of auriculo–ventricular conduction, marked depression of the sinus node, and sinus arrest. These changes may easily terminate in cardiac arrest, particularly in patients suffering from jaundice, perforated peptic ulcer, and sinus bradycardia. In 2 of the 5 reported cases the patients were jaundiced.

In the authors' cases the response to intravenous administration of atropine was striking, showing runs of ventricular tachycardia and in one case a short burst of ventricular flutter. Several possible theories of these results are discussed. The tracings do not support the contention that atropine, by causing central vagal stimulation, potentiates the cholinergic action of neostigmine on the heart. The authors suggest that deaths following injection of neostigmine are attributable to either (1) the cardio-inhibitory action of neostigmine, or (2) the adrenergic effect of neostigmine and atropine, resulting in ventricular fibrillation. *W. Stanley Sykes*

A Physiologic and Clinical Study of Cardio-Vascular Diseases. ALDO A. LUISADA, M.D. Pp. xlv+680, with 312 illustrations. Second edition. Price 114*s*. London: Baillière, Tindall & Cox.

This book has been extensively rewritten to cover the advances during the six years since the previous edition and there are new chapters on cardiovascular syphilis, prognosis of cardiovascular disease, and the social and legal aspects of heart disease. There are three appendices on prescriptions mostly of proprietary drugs, diets, and a summary of treatment in cardiovascular emergencies. Throughout the book there is more emphasis on technical and graphic methods of investigation such as phonocardiography than on physical examination, the importance of which the author considers has decreased since the newer methods of investigation have become available. The arrangement of the book is based on an anatomical rather than an ætiological classification of diseases and this has led to a great deal of repetition particularly as far as treatment is concerned. It is disappointing in a book with this title to find no adequate account of the hæmodynamic changes in heart failure or of present views on the pathogenesis of failure, one short chapter of 14 pages only being devoted to the whole of heart failure, including the manifestations, complications, diagnosis, prognosis, and treatment. The book is freely illustrated although some of the sketches are not very happily drawn, particularly the patient with a typical attack of angina pectoris who is shown clutching his left mammary region and left axilla. The bibliography is unusually complete and covers very adequately both the European and American papers.

G. W. Hayward

Comparison of the Oxygen Tension in Blood from the Left Atrium and a Systemic Artery. V. O. BJÖRK, G. MALMSTRÖM, and L. G. UGGLA. *Amer. Heart J.*, **48**, 8–12, July, 1954.

The authors have compared the oxygen tension in systemic blood with that in blood from the left atrium. In 11 cases of mitral stenosis blood drawn from the left atrium (through a long paravertebral needle) was found to have an oxygen tension which was on the average 7 mm. Hg higher than that in a systemic artery. The difference, it is suggested, might result from admixture of Thebesian-vein blood in the left ventricle. In the same patients pulmonary capillary blood, drawn through a wedged pulmonary arterial cather, had an oxygen tension averaging 21 mm. Hg higher than that in the left atrium. Here the factors involved might be: (1) double passage of blood through the alveoli leading to better oxygenation, or (2) bronchial venous admixture in the pulmonary veins lowering the oxygen content of blood reaching the left atrium. *J. McMichael*

The Second European Congress of Cardiology will be held in Stockholm, September 10–14, 1956. *The general secretary will be*

Dr. Karl Erik Grewin,
Sodersjukhuset
Stockholm S, Sweden

but further details are not yet available.

EISENMENGER'S COMPLEX

BY

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From the Regional Cardio-Vascular Centre, City General Hospital and the University Department of Medicine, Royal Hospital, Sheffield

Received November 4, 1954

Following the description by Eisenmenger in 1897 of a cyanosed man, aged 32, with a ventricular septal defect and dextroposition of the aorta without pulmonary stenosis, Abbott (1927) termed this the Eisenmenger type of congenital anomaly. Since that time a diagnosis of Eisenmenger's complex has become well established for those rare cases of cyanotic congenital heart disease with ventricular septal defect and dextroposition of the aorta without pulmonary stenosis. Although it may be difficult to differentiate this complex anatomically from ventricular septal defect with pulmonary hypertension and right ventricular hypertrophy on the one hand, and from partial transposition of the great vessels with overriding aorta on the other, it appears worthwhile preserving the term Eisenmenger's complex as a diagnosis in cyanosed patients with an overriding aorta but without pulmonary stenosis.

Clinical, electrocardiographic, and radiological findings in seven such patients are presented below together with the results of angiocardiography and cardiac catheterization. Autopsy findings were available in one patient. These patients were selected according to the criteria described above, but it became obvious from further examination that they all had in addition clinical evidence of pulmonary hypertension. Indeed, the clinical picture common to all patients with Eisenmenger's complex is one of cyanotic congenital heart disease with pulmonary hypertension.

TABLE I

CLINICAL FEATURES OF 7 PATIENTS WITH EISENMENGER'S COMPLEX

Case No.	Age and sex	Systemic blood pressure (mm. Hg)	Central cyanosis*	Cardiac murmurs
1	16 F	110/70	On exertion*	Soft systolic murmur at apex and in tricuspid area
2	16 F	110/85	Slight	Basal diastolic murmur
3	14 F	115/90	Slight	Soft apical systolic murmur
4	50 M	155/125	Marked	None
5	26 M	140/100	Slight	None
6	26 F	115/75	Slight	None
7	26 M	110/60	Slight	None

* The fingers were clubbed in all except Case 1.

Symptomatology. The dominant symptom in all seven patients was progressive breathlessness on exertion which usually appeared first during adolescence. In Case 7 dyspnœa on exertion was

* Leverhulme Research Scholar, Royal College of Physicians.

first noticed when the patient was ten years old but there was a progressive increase in its severity from the age of eighteen years until his death at the age of twenty-four.

Blueness of the lips had been noticed in cold weather by all but one of the patients (Case 6) and Case 2 had observed the cyanosis to be worse on exertion. Only in Case 4 was the cyanosis present before adolescence and in this patient it was noted at birth.

Case 1 occasionally had syncopal attacks on standing. Two other patients (Cases 2 and 4) complained of giddiness but had not at any time had attacks of unconsciousness.

Hæmoptysis occurred in Cases 5, 6, and 7. In the latter this appeared at the age of seven years and when cough and breathlessness on exertion later developed he was suspected of having tuberculosis. He had further hæmoptyses at the age of twenty-one and one month before his death.

Cases 5, 6, and 7 had chronic unproductive coughs while Case 1 had a productive cough. Two patients (Cases 1 and 3) complained of aching, præcordial pain unrelated to exertion. Case 5 had noticed finger clubbing and complained of palpitation.

Signs. All the patients had clinical evidence of pulmonary hypertension judged from giant " a " waves in the jugular venous pulse, a palpable second pulmonary sound, a systolic lift over the right ventricular outflow tract, a right ventricular heave, and a loud split second pulmonary sound. The other clinical features are shown in Table I.

Electrocardiography. The cardiogram showed the ventricular pattern of right ventricular hypertrophy and clockwise rotation of a vertical heart (Fig. 1) in all except Case 4 where systemic hypertension was present and there was clockwise rotation of a horizontal heart but no cardiographic evidence of right or left ventricular dominance.

Radiological Examination. The postero-anterior teleradiograms of six of the present group of patients are reproduced in Fig. 2, 3, and 4. Right ventricular hypertrophy was present in all cases and the other radiological features are summarized in Table II.

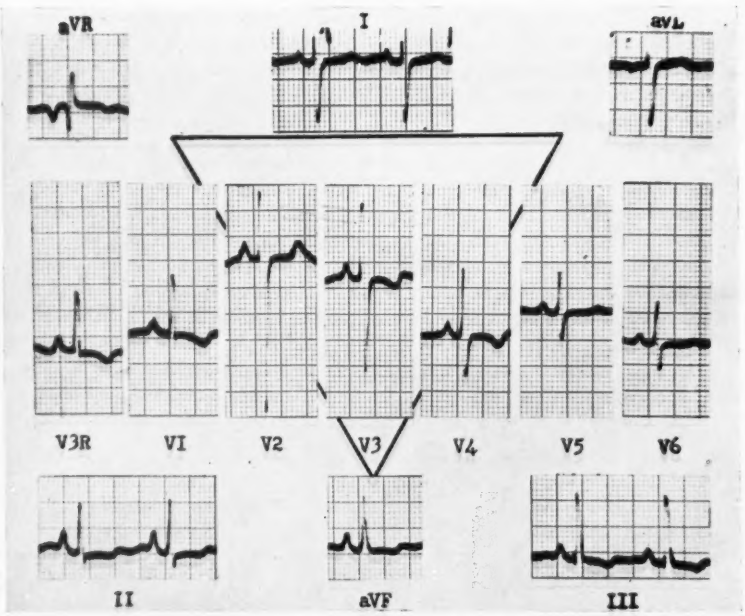

FIG. 1.—Case 6. Electrocardiogram showing ventricular pattern of right ventricular hypertrophy and clockwise rotation of a vertical heart. Similar electrocardiograms were recorded in the other cases with the exception of Case 4.

TABLE II

RADIOLOGICAL FEATURES OF 7 PATIENTS WITH EISENMENGER'S COMPLEX

Case No.	Cardiac enlargement	Prominence of pulmonary artery and main branches	Increased pulsation of pulmonary arteries
1	Marked	Moderate	Absent
2	Slight	Moderate	Absent
3	None	Moderate	Present
4	Slight	Slight	Present
5	Moderate	Moderate	Present
6	Slight	Slight	Present
7	Slight	Moderate	Absent

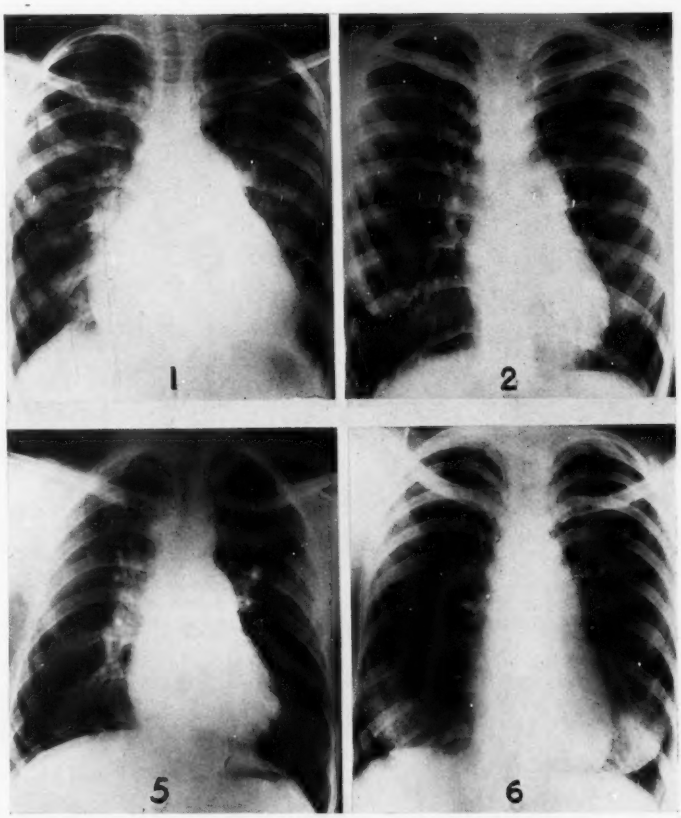

FIG. 2.—Postero-anterior teleradiograms of four patients (Cases 1, 2, 5, and 6) with Eisenmenger's complex.

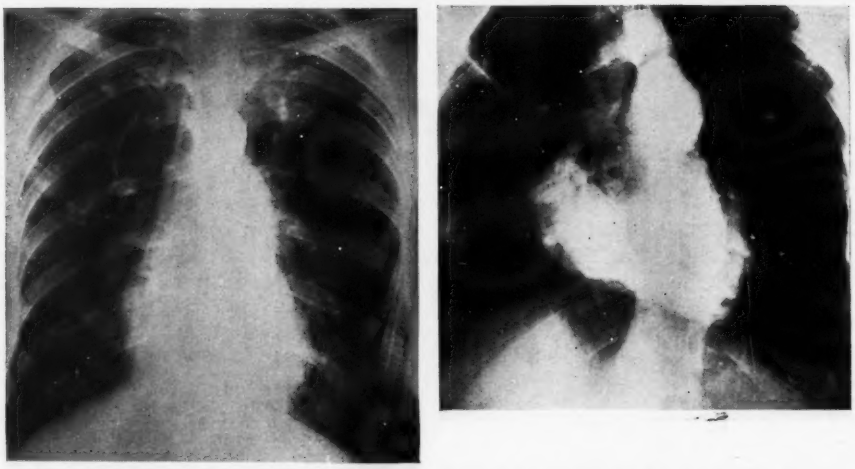

FIG. 3.—Case 7. The antero-posterior angiocardiogram, reproduced on the right, shows simultaneous filling of the pulmonary arteries and the ascending aorta from the right ventricle 3 sec. after the injection of the contrast medium. The postero-anterior teleradiogram is shown on the left.

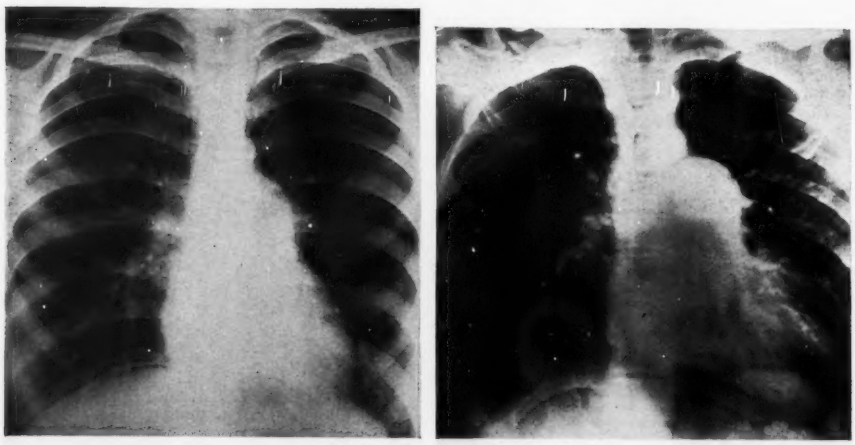

FIG. 4.—Case 3. The antero-posterior angiocardiogram, reproduced on the right, shows simultaneous filling of the pulmonary arteries and the ascending aorta from the right ventricle 3 sec. after the injection of the contrast medium. The postero-anterior teleradiogram is shown on the left.

Angiocardiography. Angiocardiographic examination was carried out in all seven patients. In each one there was simultaneous early filling of the ascending aorta and pulmonary artery by contrast medium from the right ventricle, indicating that there was an overriding aorta (Fig. 3 and 4). In all, the pulmonary artery and its main branches were dilated and there was no evidence of pulmonary stenosis. A patent ductus arteriosus was subsequently demonstrated in Case 6 by cardiac catheterization. This patient has already been reported by Whitaker *et al.* (1955) as a case of patent ductus arteriosus with severe pulmonary hypertension associated with an overriding aorta, since it was considered that the density of the contrast medium in the ascending aorta was

too great to be due to regurgitation of dye entering the aorta through the patent ductus (Fig. 6, Whitaker *et al.*, 1955).

Cardiac Catheterization. Cardiac catheterization was carried out in six patients. In all these the tip of the catheter was passed into the pulmonary artery. Pressures were recorded and blood samples taken as the catheter was withdrawn through the cardiac chambers. Results of these observations are shown in Table III. In Case 6 the tip of the cardiac catheter passed through a patent ductus arteriosus into the descending aorta.

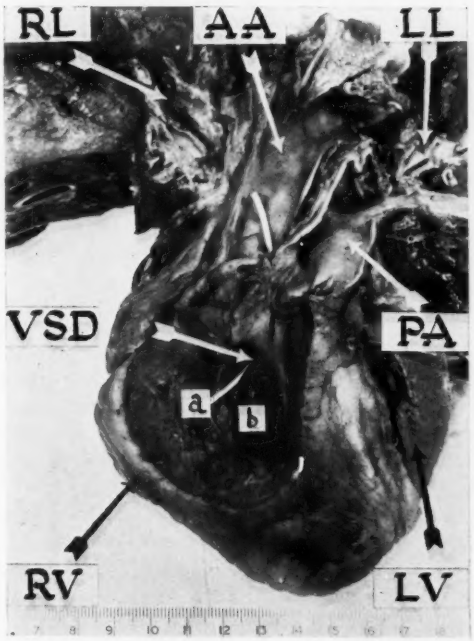

FIG. 5.—Case 7. The light indicator (*a*) has been passed from the hypertrophied right ventricle behind the crista supraventricularis into the overriding ascending aorta. The dark indicator (*b*) has been passed from the right ventricle through a ventricular septal defect in the membranous part of the septum into the left ventricle. RL=Right lung. LL=Left lung. AA=Ascending aorta. PA=Pulmonary artery. VSD=Ventricular septal defect. RV=Right ventricle. LV=Left ventricle.

FIG. 6.—The light indicator (*a*) has been passed from the right ventricle through a ventricular septal defect in the membranous part of the septum into the left ventricle. The dark indicator (*b*) has been passed from the left ventricle into the ascending aorta and in this case the crista supraventricularis has been removed (Case 7). RL=Right lung. LL=Left lung. AA=Ascending aorta. PA=Pulmonary artery. VSD=Ventricular septal defect. RV=Right ventricle. LV=Left ventricle.

NECROPSY FINDINGS IN CASE 7

The heart was enlarged mainly due to hypertrophy of the right ventricle. The thickness of the right ventricular wall was 12 mm. and that of the left 8 mm. There was an overriding aorta and a high ventricular septal defect which was concealed behind a much hypertrophied crista supraventricularis. The aorta took origin from both ventricles. The origins of the coronary arteries were abnormal. The right arose from the anterior aortic cusp and the left from the right posterior cusp. There was no patent ductus arteriosus nor atrial septal defect and the aortic arch was left-sided. There were flecks of atheroma on the pulmonary artery (Fig. 5 and 6).

On histological examination of the elastic intrapulmonary arteries atheroma was noted in the

intima. The muscular pulmonary arteries (1–0·1 mm.) showed widespread severe changes consisting of medial hypertrophy and obliteration of the lumen by fibrous tissue which had proliferated from the sub-intimal region. The elastic laminæ were thick and wavy in appearance. The arterioles showed similar changes to these in the media and intima. The small pulmonary veins appeared to be normal with no evidence of thrombosis or sclerosis (Fig. 7 and 8).

FIG. 7.—Transverse section of muscular pulmonary artery. There is proliferation of fibrous tissue in the intima. The media is hypertrophied and both elastic laminæ are thick. The lumen has been obliterated (Case 7). Stained with Verhoeff/Van Gieson. Magnification, × 178.

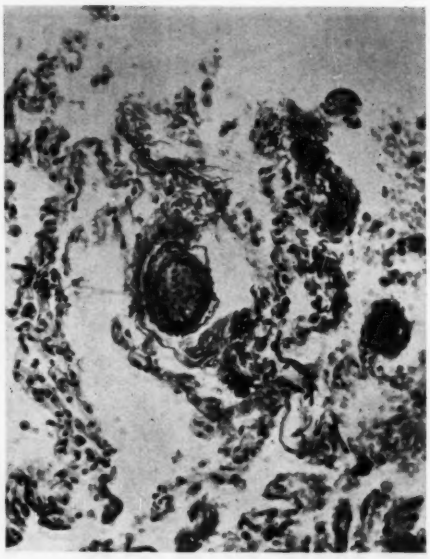

FIG. 8.—Transverse section of pulmonary arteriole. There is proliferation of intimal fibrous tissue, obliterating the lumen. The media is hypertrophied (Case 7). Stained with Verhoeff/Van Gieson. Magnification, × 178.

DISCUSSION

Symptomatology. Progressive dyspnœa on exertion from adolescence is one of the major symptoms of this anomaly. In all our patients and in one reported by Hurst and Schemm (1948) the symptoms first appeared during adolescence but in another patient reported by Bond (1951) it was already present at the age of three and a half years. From a histological study of the pulmonary arteries in a child of eleven months with Eisenmenger's complex, Edwards (1954) believes that the onset of dyspnœa is related to the development of intimal changes in the pulmonary arteries from pulmonary hypertension.

In Bond's (1951) review of 18 patients with Eisenmenger's complex neither hæmoptysis nor cough were noted. This is unexpected since both are common complaints when pulmonary hypertension complicates other anomalies such as patent ductus arteriosus and mitral stenosis. However, three of the present patients had hæmoptysis and four had chronic cough, and these symptoms, which are probably manifestations of abnormally high pulmonary vascular blood pressures, appear to be characteristic but not diagnostic of Eisenmenger's complex.

Although syncopal attacks occurred in one of our patients they may have been coincidental since there appears to be no obvious explanation of these.

Hoarseness and aphonia were present in cases reported by Baumgartner and Abbott (1929)

and by Millman and Kornblum (1936) and were considered to be due to the pressure of the dilated pulmonary vessels on the recurrent laryngeal nerve. None of our patients had such symptoms and the explanation probably is that none of them had extreme dilatation of the pulmonary arteries such as has been noted by Campbell (1951) in Eisenmenger's complex.

Signs. Although Bing's (1947) observations show that pulmonary hypertension occurs in Eisenmenger's complex, it has not been stressed that the clinical manifestations of this state are a feature of the complex. However, since pulmonary hypertension was recognized from its classical clinical signs in all patients in the present series such signs must be considered characteristic but not diagnostic of Eisenmenger's complex.

All the patients in the present series had central cyanosis since it is by definition a feature of the anomaly. This had been present from birth in Case 4 and was marked in this patient. In the others, the cyanosis developed during adolescence and was always slight. Such a late onset of cyanosis appears to be a common feature of Eisenmenger's complex and has been noted previously by Stewart and Crawford (1933) and by Bond (1951). However, early onset of cyanosis does not exclude the diagnosis since it was present at birth in a patient reported by Glazebrook (1943) and in Case 4 of the present series. Abbott (1927) and Taussig and Semans (1940) diagnosed Eisenmenger's complex in patients who were not cyanosed. Although, as the present series shows, most patients who eventually fulfil the criteria for a diagnosis of Eisenmenger's complex are acyanotic for many years, it is difficult in the acyanotic phase to recognize an overriding aorta which is an essential component of the complex. Before the onset of cyanosis such cases are indistinguishable from patients with ventricular septal defect and pulmonary hypertension unless there is sufficient shunt into the aorta from the right ventricle for this to be evident on angiocardiography. The late onset of cyanosis is more probably related to the development of polycythæmia than to any great change in the magnitude of the shunt from right ventricle to aorta, since even in patients with frank central cyanosis there is not a severe degree of arterial oxygen unsaturation (Table III). Bond (1951) states that polycythæmia is uncommon in this condition but the present series indicates that there may be a severe degree of polycythæmia in some patients (Table III).

TABLE III

RESULTS OF CARDIAC CATHETERIZATION IN 6 PATIENTS WITH EISENMENGER'S COMPLEX

Case No.	Blood hæmoglobin content (g. per 100 ml.)	Hæmatocrit	Blood oxygen percentage saturation						Pulmonary artery blood pressure (mm. Hg)
			Superior vena cava	Inferior vena cava	Right atrium	Right ventricle	Pulmonary artery	Arterial	
1	12·9	50	35	45	36	31	34	95	130/80
2	16·0	49	71	72	69	76	71	82	90/55
3	16·0	47	71	75	68	72	72	87	75/40
5	15·9	54	71	62	71	70	71	91	135/75
6	18·1	58	70	71	70	71	75		125/80
7	19·5	60	—	—	76	—	75	92	Mean 90

Case 4 was not investigated by cardiac catheterization. In this case, the blood hæmoglobin content was 17 g. per 100 ml. and the hæmatocrit 68 per cent. He has died since this paper was written and necropsy confirmed the diagnosis.

It was shown by Burwell (1942) that the arterial oxygen saturation increased when pure oxygen was breathed. This, they believed, indicated that cyanosis was in part produced by incomplete oxygenation of blood in the lungs due to a congenital abnormality of the pulmonary epithelium or capillaries. If incomplete æration of the blood in the lungs were a cause of the arterial blood

oxygen unsaturation it would be expected that there would also be carbon dioxide retention, of which Platts and Whitaker (1954) found no evidence. Voci *et al.* (1952) and Goldberg *et al.* (1951) obtained pulmonary venous blood samples in patients with Eisenmenger's complex and found that the oxygen saturation of the samples was normal. The former authors obtained these blood samples by passing a cardiac catheter through an associated atrial septal defect while the latter observers catheterized anomalous pulmonary veins entering the right atrium. It seems that the unsaturation of arterial blood is due entirely to mixed venous blood entering the aorta from the right ventricle.

Previous authors have emphasized the importance of a left parasternal systolic murmur in the diagnosis of Eisenmenger's complex. A systolic murmur, maximal in the second to fourth left intercostal spaces, was noted in 14 of the 18 cases reviewed by Bond (1951) who considered that a systolic murmur should be expected in every case. However, as 5 of the 7 patients in the present series had no systolic murmurs and 4 of these no murmurs at all, it is impossible to attach great diagnostic importance to a systolic murmur, especially as this was insignificant in the two patients where it was present (Table I). It must be emphasized that a parasternal systolic murmur is not an essential feature and not even a common feature of the clinical picture of Eisenmenger's complex. In view of this it seems relatively unimportant to discuss the radiation of such murmurs in their differentiation from the murmurs of Fallot's tetralogy as has been done previously by Bond (1951), who believes that the systolic murmur of Fallot's tetralogy radiates to the neck whereas that in Eisenmenger's complex does not. Such difference in radiation as exists is most probably related to the intensity of the murmur which is usually greater in the tetralogy. However, in cases such as that of Wood (1950), where there was a basal systolic murmur of such intensity as to produce a thrill in the third left intercostal space, any real difference in radiation would be of diagnostic importance.

Electrocardiography. Bond (1951) found left axis deviation in one case of Eisenmenger's complex and stated that the usual cardiographic findings are normal or left axis deviation or occasionally right axis deviation. However, more recently Wood (1950), Kaplan and Robinson (1954), and Edwards *et al.* (1954) have emphasized that cardiographic evidence of right ventricular hypertrophy is a feature of the anomaly. This latter view is in accord with the findings in the present series where all the patients except Case 4, who had systemic hypertension, showed cardiographic evidence of right ventricular hypertrophy and clockwise rotation of a vertical heart. Unless there is some obvious cause why there should not be a right ventricular dominance such as systemic hypertension the absence of electrocardiographic evidence of right ventricular hypertrophy excludes a diagnosis of Eisenmenger's complex.

Radiological Examination. In the present series dilatation of the pulmonary arteries has not been of the extreme degree usually considered characteristic of Eisenmenger's complex and in none of the patients was there gross prominence of the pulmonary arteries such as is seen occasionally in patients with atrial septal defect or mitral stenosis with severe pulmonary hypertension (Table II, and Fig. 2, 3, and 4). However, it cannot be questioned that Eisenmenger's complex may be associated with gross dilatation of the pulmonary arteries since Campbell (1951) found that patients with this anomaly had the largest pulmonary arteries.

Abnormal pulsation of the pulmonary arteries is not of diagnostic importance since three of the seven patients in the present series had normal pulsation while none of the others had a hilar dance (Table II).

Angiocardiography. Angiocardiography demonstrates the overriding aorta and allows Eisenmenger's complex to be differentiated from other abnormalities presenting with cyanosis and pulmonary hypertension and for this reason is probably the most important diagnostic investigation (Fig. 3 and 4). Although no patients were studied before the development of cyanosis, it appears possible to diagnose the lesion in the acyanotic phase if an overriding aorta is demonstrated by angiocardiography. If in such a phase there is insufficient shunting from the right ventricle into the ascending aorta for the contrast medium to show on the angiocardiogram it is impossible

to diagnose Eisenmenger's complex. Such patients will then probably be diagnosed as having pulmonary hypertension and ventricular septal defect from the results of cardiac catheterization.

Cardiac Catheterization. Severe pulmonary hypertension, with blood pressures similar to those in the systemic arteries, can be demonstrated by cardiac catheterization in Eisenmenger's complex (Table III). Patients with Fallot's tetralogy with loud or palpable second sounds in the pulmonary area, who, on clinical examination alone, may be thought to have pulmonary hypertension, can be easily diagnosed by this investigation. However, other congenital anomalies such as atrial septal defect, ventricular septal defect, and patent ductus arteriosus associated with pulmonary hypertension and reversal of flow may not be distinguished from Eisenmenger's complex by cardiac catheterization unless the catheter passes through the defect. Although Bing's (1947) findings at cardiac catheterization in patients with Eisenmenger's complex showed that there was usually evidence of some left-to-right flow through the ventricular septal defect, with mixing of the blood in the right ventricle, there was no evidence of this in the present series, where in every patient all the samples from the right side of the heart showed similar oxygen saturations (Table III). It is apparent from the results obtained at cardiac catheterization in this series that examination of blood oxygen saturations is of little diagnostic importance. Compared with angiocardiography cardiac catheterization is not such an important diagnostic procedure.

Pathology. The anatomical components of Eisenmenger's complex have been defined by Edwards (1954) as a high ventricular septal defect in the membranous part of the septum, dextroposition of the aorta so that it arises from both ventricles above the septal defect or from the right ventricle alone, absence of pulmonary stenosis with a normal or dilated pulmonary artery, and characteristic changes in the pulmonary vascular tree. The pathological features that may occur in a patient fulfilling the criteria for a diagnosis of Eisenmenger's complex in life are not capable of more rigid definition although this includes at one extreme a ventricular septal defect with pulmonary hypertension, right ventricular hypertrophy, and an overriding aorta and at the other extreme a moderate degree of transposition of the great vessels. Lev (1953), recognizing this, subdivides Eisenmenger's complex anatomically into Eisenmenger's complex with overriding aorta and the Eisenmenger's type of transposition, as in Case 7 of the present series where there was an abnormal origin of the coronary arteries.

The pulmonary artery always arises from the right ventricle distinguishing this condition from more severe degrees of transposition. The pulmonary valves are usually normal in structure and number although Lavenne *et al.* (1954) have described associated pulmonary insufficiency due to an absence of the pulmonary valves. The pulmonary arteries are usually larger than the aorta and this is probably due to pulmonary hypertension. Such dilatation of the pulmonary arteries was noted at autopsy examination in Case 7. Calcification of the pulmonary cusps may occur (Stewart and Crawford, 1933) and infective endocarditis of the pulmonary valves has been described (Abbot, 1927; Millman and Kornblum, 1936; and Bedford and Parkinson, 1936).

The aorta may be hypoplastic although in Case 7 of this series it was normal. The aortic valves are usually normal in number but may be deformed (Eisenmenger, 1897; and Hurst and Schemm, 1948) and this may lead to aortic incompetence. The aorta may arise from both ventricles or preponderantly from the right ventricle (Barlow, 1876; Schramm, 1929; and Saphir and Lev, 1941).

Other congenital abnormalities of the heart may be associated with this complex. Bond (1951) in a review of lesions associated with Eisenmenger's complex pointed out that the following had been reported: atrial septal defect, patent ductus arteriosus, right-sided aorta, anomalous origin of vessels from the aortic arch, patent foramen ovale, coarctation of the aorta, and anomalous coronary artery distribution. In Case 6 of the present series an associated patent ductus arteriosus was demonstrated at cardiac catheterization. Brown (1950) thought that the general appearance of the heart in Eisenmenger's complex suggested that the conus and the pulmonary artery had developed normally and that the endocardial cushions of the atrial canal had, in the main, fulfilled their correct function. Rosedale (1935) considered that failure of the lower part of the bulbar arches to fuse and consequent failure of the aortic vestibule to be shifted to the left resulted in dextroposition

of the aorta. Edwards (1954) pointed out that when a probe is passed from the right ventricle through the membranous part of the ventricular septum in a normal heart it enters the ascending aorta and with any defect of the membranous septum the aorta would consequently override both ventricles. It seems probable that right ventricular hypertrophy accentuates the overriding and is largely responsible for the dextroposition of the aorta in those cases where there is no evidence of abnormal rotation of the great vessels. Right ventricular hypertrophy also produces in Eisenmenger's complex a well marked crista supraventricularis, which in Case 7 of the present series separated the conus of the right ventricle from the ventricular septal defect and origin of the aorta (Fig. 5).

The extensive changes that occurred in the muscular pulmonary arteries and the arterioles in Case 7 of this series (Fig. 7 and 8) are typical of those reported by previous observers. The combination of medial hypertrophy and intimal proliferation was noted as early as 1933 by Stewart and Crawford but their patient was aged sixty and was suffering from syphilis and it was difficult to be sure of the ætiology of the changes. Civin and Edwards (1950) noted medial hypertrophy in a child, aged eleven months, who had Eisenmenger's complex. They postulated that the medial hypertrophy was due to a persistently increased muscular tone in the pulmonary vessels and considered that this was a protective function to diminish the excessive blood flow to the lungs, which they compared to the state present in the fœtus where the right ventricle pumps blood into both systemic and pulmonary circulations and where the resistance to flow in the latter is high to prevent flooding of the lungs. They believe that the muscular hypertrophy leads to a diminution in diameter of the pulmonary vessels with a resultant increase in pulmonary pressure. The induced pulmonary hypertension brings about further intimal proliferation with a still greater reduction in the diameter of the lumen of the vessel and a still greater increase in pulmonary artery pressure. Edwards (1954) noted that the same problems were involved in cor triloculare biatriatrum, persistent runcus arteriosus with big pulmonary arteries, and coarctation of the aorta with a patent ductus arteriosus in which the ductus enters the aorta distal to the coarctation. Old and Russell (1950) described similar histological findings in a boy, aged eleven, without Eisenmenger's complex but also noted the presence of arterial necrosis.

Differential Diagnosis

The differential diagnosis of the present anomaly is from other cyanotic conditions associated with pulmonary hypertension. A long history of recurrent pulmonary infection and signs of pulmonary hypertension and cyanosis may suggest a diagnosis of chronic pulmonary heart disease but, as pointed out by Platts and Whitaker (1954), the absence of carbon dioxide retention will exclude this.

Patients with an atrial septal defect complicated by pulmonary hypertension and reversal of the flow through the defect, will have more marked cardiac enlargement and larger pulmonary arteries than the patients in the present series, but may be confused with those patients with Eisenmenger's complex having extreme dilatation of the pulmonary arteries. Angiocardiography will clearly demonstrate the septal defect for, when there is reversal of flow, there is early filling of the left atrium by contrast medium. In such cases the cardiac catheter usually passes with ease through the septal defect.

The differentiation of the present anomaly from ventricular septal defect with pulmonary hypertension where the defect is in the membranous part of the septum is a problem of definition. Where the right ventricular pressures are sufficiently high to cause blood to pass from the right ventricle into the aorta, which may be evident on angiocardiographic examination or from the presence of cyanosis, such patients fulfil the criteria for a diagnosis of Eisenmenger's complex. When there is a ventricular septal defect in the muscular part of the septum complicated by pulmonary hypertension so that the dominant flow is from the right to the left ventricle, it may be possible to recognize that such patients have not an overriding aorta from early filling of the left ventricle on angiocardiography.

Patent ductus arteriosus with severe pulmonary hypertension and reversal of the flow can be differentiated from the present anomaly by angiocardiography and cardiac catheterization. Angiocardiograms in patients with Eisenmenger's complex show early filling of the overriding aorta while in patients with patent ductus arteriosus and severe pulmonary hypertension there is usually early filling of the descending aorta from the pulmonary artery. On cardiac catheterization it is usually possible to pass a catheter through the ductus when this is associated with severe pulmonary hypertension and reversal of flow. The problem of differentiation may, however, be impossible since it is apparent that an overriding aorta and patent ductus arteriosus may co-exist in cyanotic patients with pulmonary hypertension as in Case 6 in the present series.

Since the majority of patients with Eisenmenger's complex develop cyanosis during adolescence, there is rarely any difficulty in differentiating this anomaly from transposition of the great vessels where cyanosis is present from birth. However, in those patients with Eisenmenger's complex who are cyanosed from birth such a differentiation is necessary and can usually be made from the lateral angiocardiograms when the diagnosis of transposition is made if the pulmonary artery appears to arise from the left ventricle.

Since many of the patients with Eisenmenger's complex present no sign other than those of cyanosis and pulmonary hypertension they may be regarded from clinical, electrocardiographic, and radiological examination as cases of primary pulmonary hypertension. The true nature of the congenital anomaly will become apparent when an overriding aorta is demonstrated by angiocardiography.

Patients with Fallot's tetralogy with loud and even palpable sounds in the pulmonary area may be considered, on clinical examination, to have cyanotic congenital heart disease and pulmonary hypertension and, possibly, Eisenmenger's complex. Such patients, however, are decisively differentiated by measurement of the pulmonary artery blood pressure.

SUMMARY

A description is given of seven patients with Eisenmenger's complex. This is a clinical rather than an anatomical diagnosis appropriate for patients with cyanotic congenital heart disease with pulmonary hypertension and an overriding aorta.

The symptoms and signs associated with this anomaly are characteristic but not diagnostic of it since they occur in other forms of cyanotic congenital heart disease with pulmonary hypertension. Breathlessness on exertion, hæmoptysis, and chronic cough were the common symptoms. Hoarseness and aphonia did not occur in the present series.

The only physical signs common to this group of patients, other than cyanosis which was present by definition, were those of pulmonary hypertension. Cyanosis developed during adolescence except in one patient where it was present from birth. Four patients had no mumurs. A parasternal systolic murmur is not an essential feature and in this series was not even a common feature of the clinical picture.

On electrocardiographic examination there was evidence of right ventricular dominance in all patients except one who had also systemic hypertension.

On radiological examination there was evidence of right ventricular hypertrophy and dilatation of the pulmonary arteries which was not of the extreme degree usually considered characteristic of Eisenmenger's complex. Angiocardiography was the most important diagnostic investigation in this anomaly since it demonstrated the overriding aorta. Cardiac catheterization confirmed the presence of pulmonary hypertension.

The anatomical features that may occur in patients fulfilling the criteria for a clinical diagnosis of Eisenmenger's complex are discussed.

On histological examination medial hypertrophy and intimal changes in the pulmonary arteries and arterioles, which occur in other forms of congenital heart disease with pulmonary hypertension, are characteristic of this anomaly.

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The patient referred to as Case 4 has died and necropsy has confirmed the diagnosis of Eisenmenger's complex.

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DISSOCIATION WITH INTERFERENCE, RECIPROCAL RHYTHM, AND CORONARY SINUS RHYTHM

BY

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Dissociation with interference and reciprocal beats have many features in common. They have to be differentiated from one another and from auricular parasystole. Herrmann and Ashman (1930) stressed the importance of the auricular rhythm and polarity of the P waves in the bipolar limb leads as differential criteria between the two rhythms, regular auricular rhythm and positive P waves indicating dissociation with interference. Either may occur when the auriculo-ventricular node is an independent pacemaker, or more rarely, when there is a heterogenetic centre of impulse formation in the ventricles. In both orthograde conduction remains intact although it may be impaired. Retrograde conduction is completely blocked in dissociation with interference whereas in reciprocal rhythm it is not altered, although for reciprocal beats to occur it is usually delayed to a certain critical level. The recognition of these disturbances of conduction is important in clinical medicine, for most reported cases have underlying organic heart disease, or are caused by intoxication such as that due to digitalis or to an increased content of pressor substances in the blood. Their presence can only be detected by graphic methods, and on ordinary clinical examination they are likely to be confused with sinus rhythm, or an idioventricular rhythm with extrasystoles in the ordinary sense. Thus either rhythm may be responsible for one variety of pulsus bigeminus.

As early as 1897 Cushny confirmed the existence of two separate foci of stimulus formation in the heart acting simultaneously, the slower rhythm at times interfering with the faster centre of impulse formation: his calculations were made from canine myocardiographic tracings. Later Rothberger and Winterberg (1910), using the electrocardiograph, noted that transient dissociation with interference occurred in the dog's heart during the development of nodal rhythm. In 1923, Mobitz established dissociation with interference as a pararrhythmia *sui generis*. It is characterized by the co-existence of two separate foci of stimulus formation in the heart, usually a slow sinus rhythm and a faster nodal rhythm, the slower rhythm at times interfering with the faster rhythm by conducted beats. These conducted beats form the only link between the two centres, and they occur when a sinus impulse reaches the ventricles outside their refractory period. As in parasystole the slower pacemaker is protected against the faster nodal centre by an entrance block. With regard to reciprocal beats, Decherd and Ruskin (1943), have applied the experimental findings of Schmitt and Erlanger (1928) regarding uni-directional block to explain their return mechanism. They postulate an area of refractoriness in the vicinity of the auriculo-ventricular node, to the neighbourhood of which the impulse returns or sends back a subsidiary impulse to the ventricles. Reciprocal beats are only found in nodal rhythm with pre-ventricular activation.

In clinical practice dissociation with interference is usually observed as a transient phenomenon during the course of changing rhythm, although it may be present over several years (Schott, 1951). Digitalis is an important causative agent, but usually only in the presence of organic heart disease. Schott (1937), however, noticed that small doses of the drug abolished the rhythm in one case. Rheumatic carditis may be the cause of either rhythm. Bain (1939) and Stein and Bartlett (1946) have published cases of dissociation with interference during active rheumatic carditis, and Dock's

case (1928) showing reciprocal rhythm had mitral valve disease. Dissociation with interference is also reported as a feature of coronary insufficiency (Heard and Colwell, 1916; White, 1916; and Burchell, 1949.) Burgess *et al.* (1936), and Espersen and Jorgensen (1947) have reported the par-arrhythmia during the hypertensive crises of phæochromocytoma, presumably due to the increased content of pressor amines in the blood.

Case 1. Dissociation with Interference

In July, 1951, a man, aged 27 years, was under investigation for symptoms other than cardiovascular. A routine electrocardiogram, however, revealed marked intra-auricular block and complete left bundle branch block (Fig. 1). The lesions in the conducting tissues were considered static and most probably the result of past rheumatic carditis. He was not seen again until May, 1954, when he was admitted to hospital with congestive heart failure. The pulse was very slow and intermittent and on auscultation auricular contractions were clearly audible. A tentative diagnosis of complete auriculo-ventricular dissociation was made compli-

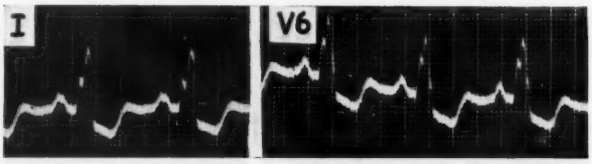

Fig. 1.—Case 1. Intra-auricular block, and left bundle branch block. Time marker 0·04 sec.

cated by ' extrasystoles ' in the ordinary sense of the word. Electrocardiography, however, confirmed that the correct diagnosis was dissociation with interference. Subsequently serial electrocardiography was carried out using long strips of lead II to determine the course of changing rhythm. Cuttings from these records are shown in figures of this case, and Table I records the average values of the measurements calculated from the long records taken. There is a marked sinus bradycardia, probably due to 2:1 sino-auricular block, which is

TABLE I

Dissociation with Interference.—Case 1

Fig. No.	1	2	3	4	5	6
Rhythm	Sinus rhythm	Dissociation with interference	Dissociation with interference	Sinus bradycardia	Complete A-V dissociation	Sinus rhythm auricular extrasystoles
P–R	0·2	—	—	0·24		0·18–0·26
Ventricular rate	69·7	48·4	44·4	51	34	44
Auricular rate	69·7	42·8	40	51	66	44
Cycle length	0·86	1·24	1·35	1·16	1·74	1·36
Cycle length after conducted beats	—	1·24	1·35	—	—	—

the true cause of the dissociation with interference. The auricular rate varies between 39 and 77 beats a minute, and the ventricular rate between 33 and 71. Amyl nitrite increased the auricular rate to 48 beats a minute abolishing the conducted beats (Fig. 2) but it had no influence on the ventricular rate. This should be compared with Case 2 (Fig. 10) where this drug caused a marked nodal tachycardia. Dissociation with interference was first noted (Fig. 2) five days after the patient had received 0·5 mg digoxin daily, and it was

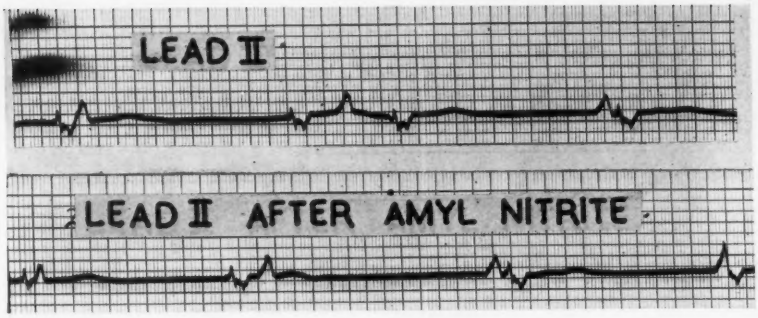

FIG. 2.—Case 1. Effects of amyl nitrite. Dissociation with interference. Upper tracing control. Time marker 0·02 sec.

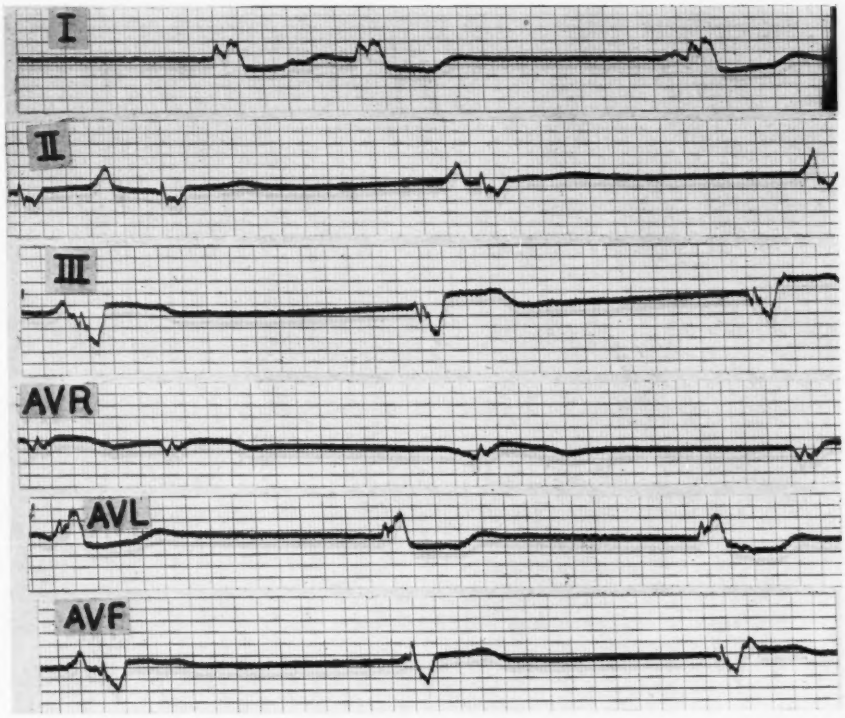

FIG. 3.—Case 1. Dissociation with interference with conducted beats. Time marker 0·02 sec.

found to persist five days after digitalis had been stopped, the ventricular rate having fallen from 48·4–44·4 beats a minute (Fig. 3). No further incidence of the recurrence of the pararrhythmia was recorded in the serial records of this case and it was most likely due to digitalis action. Further cardiograms recorded at intervals of a few days demonstrated sinus bradycardia with first degree heart block (Fig. 4), the P–R interval varying from 0·18–0·26 sec. Fig. 5 shows complete auriculo-ventricular dissociation with a fast sinus rate.

The last tracing (Fig. 6) was recorded when it was noted clinically that the patient's pulse was completely irregular. Multiform auricular extrasystoles with runs of auricular tachycardia (Fig. 6, 6) are seen. Frequently the P waves of the extrasystoles are inverted, the P–R intervals of these beats being 0·26 sec. Occasionally these beats occur in groups (Fig. 6, 5). Scherf and Harris (1946) distinguish such beats as coronary sinus rhythm. The coupling of the multiform extrasystoles varies from 0·92 to 1·16 sec., suggesting that each type arises from a separate auricular focus.

This case, therefore, presents varying rhythms, including dissociation with interference, complete auriculoventricular dissociation, and multiform auricular extrasystoles (including coronary sinus beats), which originate in polytopic foci in the auricles.

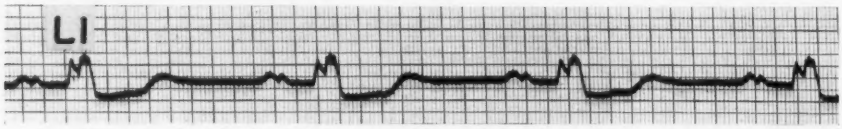

FIG. 4.—Case 1. Sinus bradycardia with first degree A-V block. Time marker 0·02 sec.

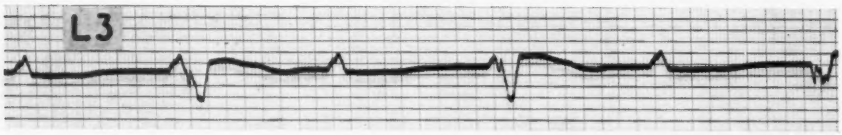

FIG. 5.—Case 1. Complete A-V dissociation. Time marker 0·02 sec.

CASE 2. RECIPROCAL RHYTHM

A man, aged 45 years, was noted to have a slow pulse in February, 1954, when he was undergoing investigation for symptoms other than cardiovascular. A routine cardiogram revealed that he had nodal rhythm with pre-ventricular activation (Fig. 7). Subsequently, during July, 1954, serial electrocardiography was carried out as the patient had developed an irregular rhythm due to the occurrence of reciprocal beats. The effects of exercise and of various drugs on the reciprocal beats were studied. Control cardiograms were done under resting conditions before each assessment, and long strips of lead II of 100 complexes or more were used for calculations. Table II represents the average values calculated from the related tracings. Reference

TABLE II

RECIPROCAL RHYTHM.—CASE 2

Fig. No.	7	8	9			10		11		12		
			A	B	C	A	B	A	B	A	B	C
Ventricular rate	42·8	42·8	35·7	50	40	50	100	40	55·5	30	40	43
P–R	—	—	—	0·16	—	—	—	—	—	0·14	0·16	—
R–P	0·08	0·1	0·18	—	0·06	0·14	0·06	0·06	0·06	—	—	0·14
R–P before reciprocal beats	—	0·2	—	—	—	0·2	—	—	—	—	—	0·32
P–R before reciprocal beats	—	0·3	—	—	—	0·32	—	—	—	—	—	0·32

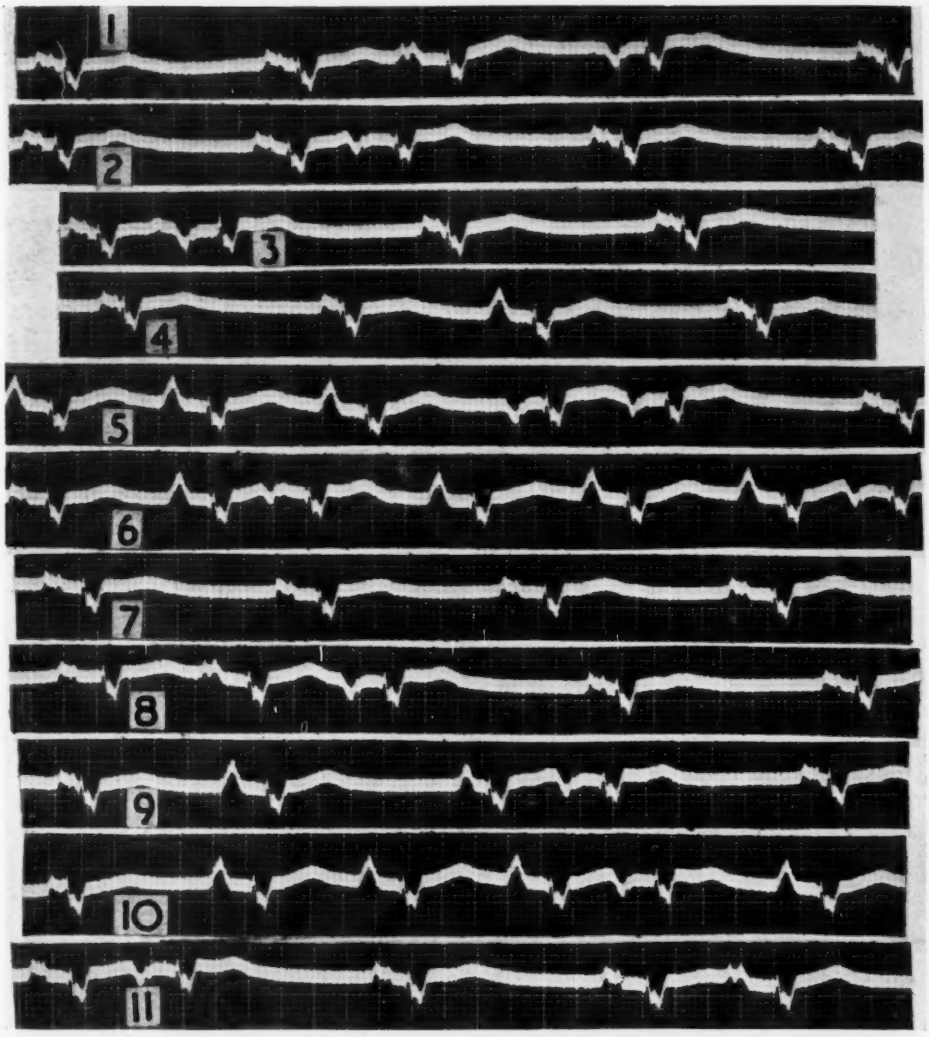

FIG. 6.—Case 1. Multiform auricular extrasystoles. Time marker 0·04 sec.

to the control records (Fig. 7, 8, 9A, 10A, and 11A) reveals that the nodal rate varies spontaneously between 35·7 and 50 beats a minute. They also show variation in the duration of the R–P interval between 0·08 sec. and just under 0·2 sec. Calculations from long tracings of over 250 complexes indicated that reciprocal beats only occurred when the R–P interval was 0·2 sec. or more, so demonstrating the importance of delayed retrograde conduction in the incidence of the re-entry mechanism. It is noted also that the rate of retrograde conduction was independent of the nodal rate under resting conditions. Thus the R–P interval of Fig. 7 is 0·08 sec. with a nodal rate of 42·8 beats a minute, whereas the R–P interval of Fig. 9A is 0·18 sec. with a slower nodal rate, and in Fig. 10A the R–P interval is 0·14 sec. with a slightly faster nodal rate. There is an

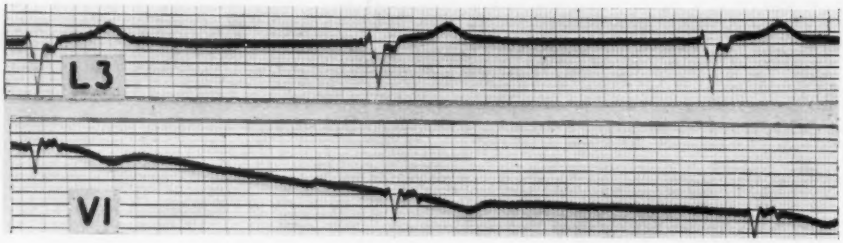

FIG. 7.—Case 2. Nodal rhythm. Time marker 0·02 sec.

inverse relationship between the R–P intervals and the P–R intervals of the reciprocal beats that follow them. In these tracings the R–P intervals are shorter than the P–R interval of the reciprocal beats. This is unusual, as it indicates that retrograde conduction takes place more readily than orthograde conduction (Gravier *et al.*, 1939; Decherd and Ruskin, 1943; Blumgart and Cargill, 1930). Fig. 12A is unique in that it shows sinus rnythm with marked bradycardia, which is most probably the true cause of the nodal rhythm. The P waves are abnormal, due to intra-auricular block. Attention is also drawn to the configuration of the complexes of lead V1 in Fig. 7 and 8. A small secondary r wave in Fig. 7 is suggestive of delayed activation of the right ventricle. The reciprocal beats of lead V1 in Fig. 8 conform to those of a complete lesion of the right bundle, and thus they reveal a latent right bundle branch block. The ventricular complexes of the reciprocal beats in all the records very in shape due to varying degrees of ventricular aberration.

The effects of strenuous exercise are recorded in Fig. 9. The control tracing has no reciprocal beats as in no incident did the R–P interval exceed 0·2 sec. Fig. 9B and C are cuttings from 100 ventricular complexes recorded immediately following strenuous exertion. The first ten complexes (Fig. 9B) demonstrate a change in the type of nodal rhythm to that with pre-auricular activation and a normal P–R association and increased nodal rate (coronary sinus rhythm, as in Fig. 6). The following complexes (Fig. 9C) confirm a reversal to the original type of nodal rhythm but with marked shortening of the R–P interval to 0·06 sec., the heart rate having returned almost to its original level. Thus exercise resulted not only in an increased nodal rate, but also speeded up retrograde conduction. These are two separate effects not dependent on one another as shown above and probably result from an increased sympathetic tone. Exercise, therefore, abolishes the reciprocal rhythm by shortening the R–P intervals. It was also noted that auricular extrasystoles occurred after exercise (Fig. 9D).

The inhalation of amyl nitrite resulted in nodal tachycardia (Fig. 10B). The nodal rate was doubled but the type of nodal rhythm was unchanged. There was shortening of the R–P intervals from 0·14 sec. to 0·06 sec. and the reciprocal beats were abolished. Before the development of nodal tachycardia, however, there was an intermediate phase of complete irregularity of the heart due to a marked increase in the number of reciprocal beats (Fig. 10B, 1 and 2), the R–P intervals in such cases remaining at 0·2 sec. Amyl nitrite therefore has two separate effects. Increased nodal rate occurs immediately and is initially associated with increased reciprocation, due to the fact that in the transient period retrograde conduction is not altered in rate, and the increased incidence of the ventricular responses increases the incidence of the reciprocal beats. In a few seconds, however, retrograde conduction is speeded up and the nodal tachycardia becomes regular with very much shortened R–P intervals.

Reports of the effects of atropine on reciprocal rhythm differ. Dock (1928) noted an increase in the incidence of reciprocal beats with prolonged R–P intervals. Bishop (1921) found atropine a specific remedy for the relief of one of his patients suffering from palpitations due to reciprocal beats. In our case we were unable to precipitate reciprocal beats by giving 1/50 grain atropine. Fig. 11B, taken after this dose records an increase in the nodal rate of 55 beats a minute from 40 beats a minute in the control. The R–P intervals remained unaltered. It may be noted that the R–P interval of the control cardiogram (Fig. 11A) is the shortest of the series (0·06 sec.), and therefore the atropine had the opportunity to reveal any effect it may have had on retrograde conduction.

The control cardiogram (Fig. 12A) before the administration of 0·25 g. quinidine demonstrates sinus rhythm with marked bradycardia and normal P–R association. Serial records were taken one hour after quinidine (Fig. 12B), and then one hour later (Fig. 12C). Quinidine suppressed the sinus pacemaker and

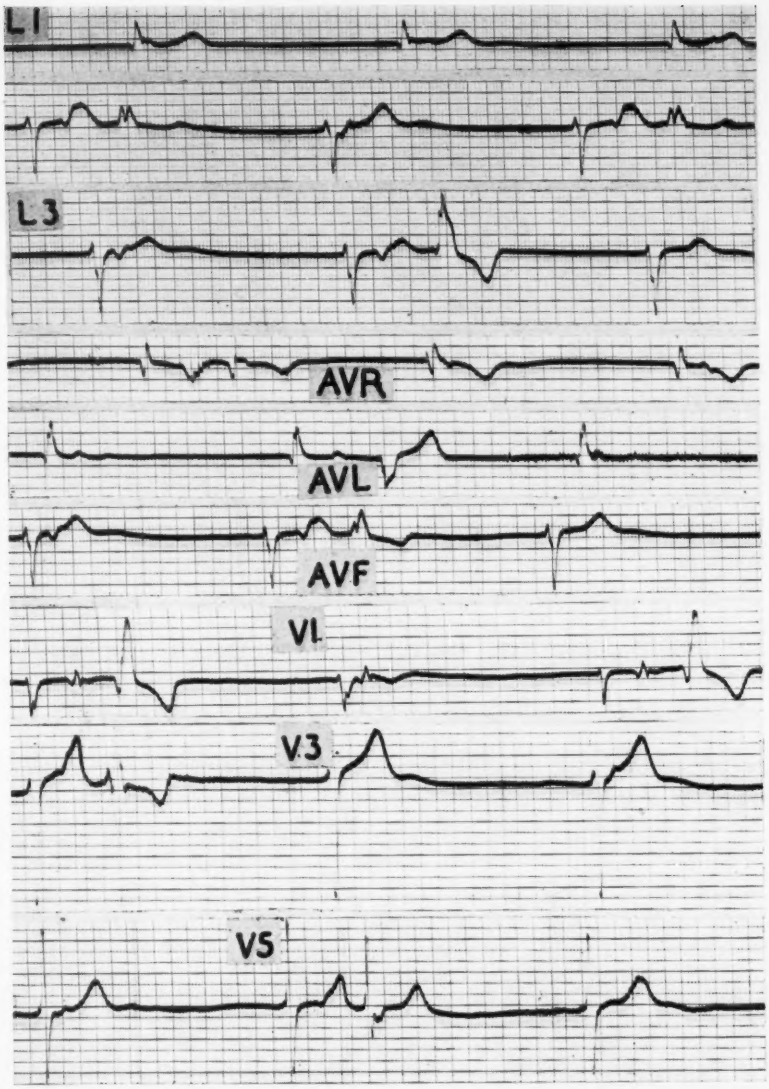

FIG. 8.—Case 2. Nodal rhythm with reciprocal beats. Time marker 0·02 sec.

incidentally increased the heart rate by transferring the pacemaker to the auriculo-ventricular node. Nodal rhythm with pre-auricular activation is recorded in Fig. 12B, and of course, no reciprocal beats. The P–R association is normal which raises the question of coronary sinus rhythm (see Case 1, Fig. 6). An hour later pre-ventricular activation with R–P intervals of 0·14 sec. occurred (Fig. 12C). Twenty reciprocal beats were recorded within 100 ventricular complexes, and the preceding R–P intervals were 0·32 sec., which are the longest of any of the series recorded. Quinidine therefore suppressed the sinus rhythm in this case causing a reversal to nodal rhythm. At first there was pre-auricular activation but after two hours,

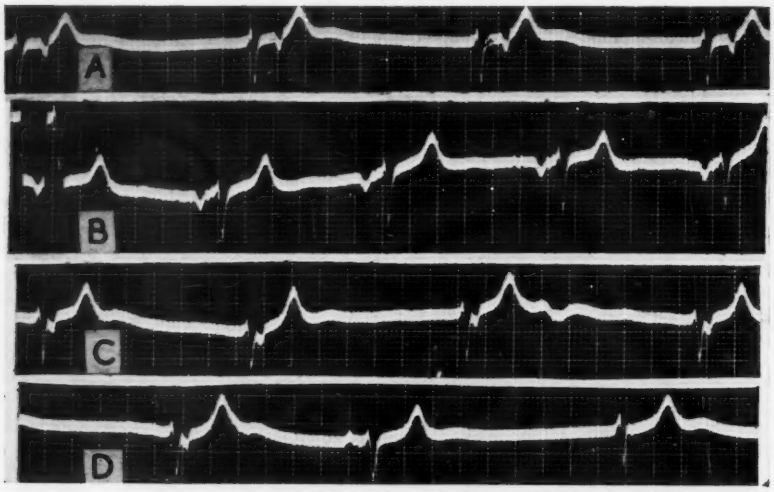

FIG. 9.—Case 2. Effects of exercise. (A) Resting control. (B) Immediately after exercise. (C) Shortly after exercise. (D) Auricular extrasystole. Time marker 0·04 sec.

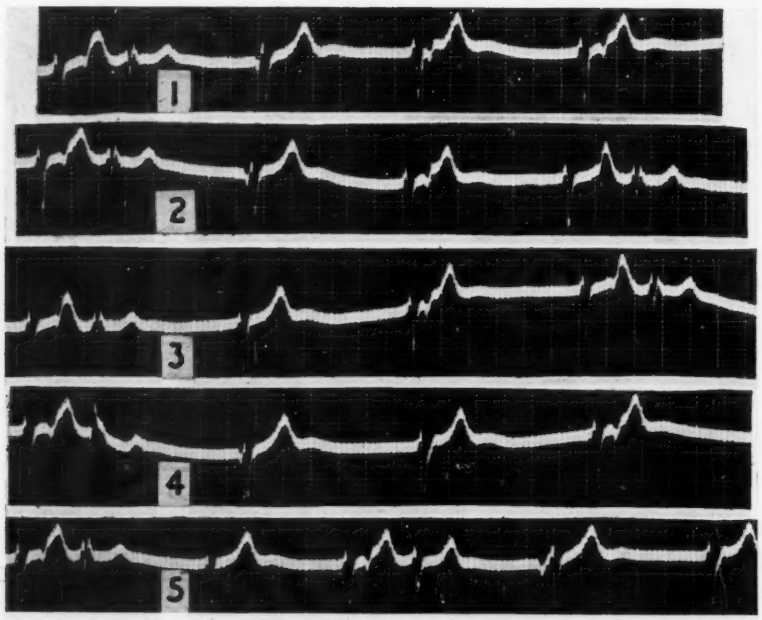

FIG. 10A.—Case 2. Control before amyl nitrite. Nodal rhythm with reciprocal beats. Time marker 0·04 sec.

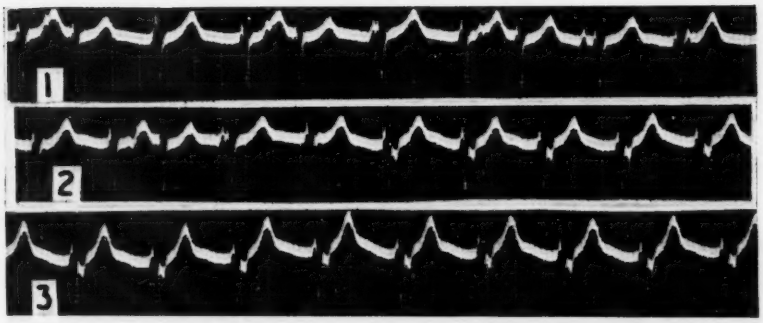

FIG. 10B.—Case 2. Effects of amyl nitrite on reciprocal beats. Time marker 0·04 sec.

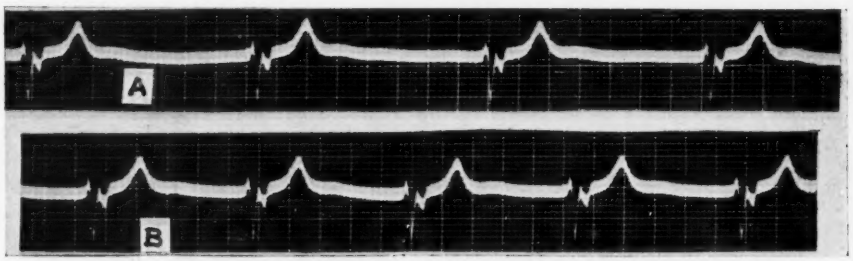

FIG. 11.—Case 2. Effects of atropine. (A) Control. (B) After grain 1/50 atropine. Time marker 0·04 sec.

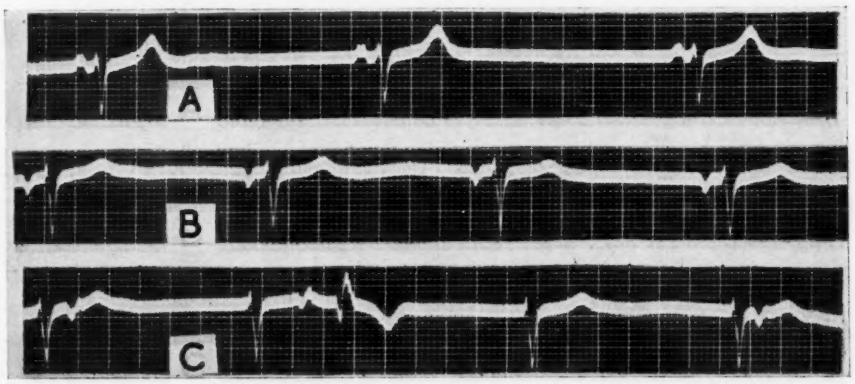

FIG. 12.—Case 2. Effects of quinidine. (A) Control. (B) One hour after quinidine. (C) Two hours after quinidine. Time marker 0·04 sec.

pre-ventricular activation occurred with prolonged R–P intervals and an increase in the incidence of reciprocal beats. Thus retrograde conduction was delayed by quinidine, but in this case there was no evidence of effect of the drug on orthograde conduction of the reciprocal beats themselves. The P–R interval of these beats (0·3–0·32 sec.) was little altered from that of the control record (Table II).

Certain additional features in these records are of basic physiological interest. Inspection of the complexes following the reciprocal beats reveals a change in the sequence of auricular and ventricular activation when compared with the complexes of the dominant rhythm. Scherf and Shookhoff (1925) demonstrated that the temporary change in the position of the P waves in the beats following the extrasystoles is dependent on the speed of conduction in the ventricles. They showed that ventricular extrasystoles which were not conducted backwards to the auricles (as reciprocal beats cannot be) were followed by complexes with pre-auricular activation in the type of nodal rhythm in this case. This apparent " shift of the pacemaker " is due to fatigue of the conducting pathways in the ventricles as the result of the extra beat, so that when the next nodal beat occurs, the auricles are found more responsive than the ventricles and pre-auricular excitation results.

The area close to the orifice of the coronary sinus has been shown to possess a high degree of automaticity (Scherf, 1944). Such coronary sinus beats have a normal P–R interval in contrast to nodal rhythm with pre-auricular activation in which the P–R intervals are greatly shortened. The P–R intervals of the extrasystoles with inverted P waves in Case 1 (Fig. 6) are 0·28 sec., and in Case 2 (Fig. 9B and 12B) the P–R intervals are 0·16 sec. (Table II). These records may therefore be interpreted as coronary sinus rhythm. However, the distinction from nodal rhythm cannot be made with certainty as disturbances of conduction may be present and these would profoundly affect the P–R association.

Clinically both cases had similar symptoms of severe upper abdominal pain attributed to pylorospasm. They were believed to be suffering from a duodenal ulcer, but special investigations failed to prove this diagnosis. However, the symptoms were severe enough to warrant laparotomy and in neither case was peptic ulceration found. Case 1 had a vagotomy which completely relieved his discomfort. The autonomic nervous system plays an important part in the production of these arrhythmias, and it is possible that a common nervous factor was responsible for the symptoms related to the gastro-intestinal tract.

Summary

Serial electrocardiographic records of two cases showing dissociation with interference, reciprocal beats, and coronary sinus rhythm are analysed. The effects of exercise and various drugs on the reciprocal beats in one case are noted. The possible correlation between the patients' symptoms and cardiac conditions are mentioned. Brief reference to some reported cases of these rare rhythms is made.

We wish to acknowledge the valuable assistance of Dr. David Scherf, New York Medical College, Professor A. D. M. Greenfield, Department of Physiology, Queen's University, Belfast, and Dr. T. H. Crozier, Electrocardiographic Department, Belfast City Hospital.

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THE SERUM CHOLESTEROL AND OTHER LIPIDS AFTER ADMINISTRATION OF SITOSTEROL

BY

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The role of cholesterol in the pathogenesis of atherosclerosis has been the subject of much investigation in recent years. The present position has been extensively reviewed by Page (1954) and Katz and Stamler (1953). In coronary artery disease a significant elevation of the plasma cholesterol and of the plasma-cholesterol/phospholipid ratio has been noted (Oliver and Boyd, 1953). The incidence of atherosclerosis has been found to be increased in countries where the diet contains a high total of fats and excessive calories (Keys, 1952). High dietary fat facilitates cholesterol absorption and vice versa (Kim and Ivy, 1952; Melinkoff *et al.*, 1950), but rigid exclusion of the fat from the diet is difficult and unacceptable to the patient. Search for other methods of reducing the blood lipids has proceeded and plant phytosterols have been reported as reducing the serum total cholesterol and changing the other serum lipids.

Sitosterol, a plant sterol, has been shown to reduce experimental hyper-cholesterolæmia in animals and birds (Pollack, 1953; Peterson, 1951). This substance is chemically related to cholesterol from which it differs by an added ethyl group in the side chain. The purpose of this study was to observe the effect of sitosterol on the serum cholesterol and other lipids in patients who suffered from coronary artery disease.

METHOD

The 26 subjects were a consecutive series in two medical units who had coronary artery disease and an initial serum cholesterol value of 230 mg. per 100 ml. or more. There was electrocardiographic confirmation of ischæmia or infarction in every case. Almost 100 per cent pure beta-sitosterol was administered orally with an unrestricted diet. This substance is a chalky gritty material insoluble in water. A palatable biscuit containing 1·5 g. was employed. Dosage of 3 g. immediately before the three main meals (9 g. daily) was continued for periods up to 21 weeks. No side effects were observed. Weekly or fortnightly estimations of the serum total cholesterol, lipid phosphorus, total lipids, and neutral fats were performed during the time of observation.

Neutral fats were calculated from the formula:

$$\text{Neutral fats} = \text{Total lipids} - [(1{\cdot}5 \times \text{total cholesterol}) + (25 \times \text{lipid phosphorus})]$$

The age and sex distribution is shown in Table I.

RESULTS

The results of the biochemical estimations are considered under the sections below.

Serum Total Cholesterol. The mean initial level was higher in the 8 women, 326 as compared to 294 mg. per 100 ml. in the 18 men (Table I). Two men showed no reduction in any reading with sitosterol. Considerable fluctuations were met with although all tests were made in mid-morning. In

TABLE I

INITIAL SERUM TOTAL CHOLESTEROL COMPARED WITH MEAN AND MINIMUM LEVELS ON SITOSTEROL REGIME

Subject	Sex	Age	Initial T.C.	Therapy T.C.		Subject	Sex	Age	Initial T.C.	Therapy T.C.	
				Mean	Minimum					Mean	Minimum
A1	M	71	260	245	135	B2	M	63	265	310	240
A2	M	66	235	261	150	B6	M	58	280	302	185
A3	M	63	230	380	275*	B8	M	52	245	227	190
A4	M	58	415	361	210	B10	M	47	365	283	215
A6	M	71	330	209	120	B15	M	46	255	222	195
A7	M	62	320	274	258	A5	F	50	300	300	245
A11	M	82	300	392	395*	A12	F	56	258	293	170
A14	M	61	305	316	175	A13	F	57	410	331	230
A15	M	58	305	232	120	B3	F	55	300	278	215
A16	M	59	265	235	235	B4	F	56	360	309	270
A18	M	63	310	235	235	B5	F	55	350	256	195
A19	M	84	280	236	165	B7	F	53	330	348	315
B1	M	56	330	268	240	B9	F	52	300	277	240

T.C.=Total serum cholesterol. *Minimum above initial value.

24 cases there was a reduction in the minimum level found under the regime and in 17 the mean level was lowered. Estimation of the means of the series showed a fall from 303 to 283 mg. per 100 ml.; this calculation was, of course, influenced by the high levels met with in the two patients mentioned above. The greatest fall in the total cholesterol was not always seen at the start of therapy and only occurred in the first two weeks in 11 of the 26 subjects.

Serum Lipid Phosphorus. The mean levels in both the sexes were 11·0 mg. per 100 ml. in the men and 11·9 mg. per 100 ml. in the women before therapy. A fall was found in the treatment period from an initial mean value of 11·3 mg. to 10·4 mg. per 100 ml. over the series (Table II). However, raised and lowered means were fairly evenly distributed, 12 being raised and 14 lowered.

Total Cholesterol–Lipid Phosphorus Ratio. No definite change was found on this value either before or during administration of sitosterol.

Neutral Fats. Raised mean levels were found in 24 out of the 26 patients. In the two subjects with a lower level during the test period, high initial readings were encountered, and both were females. One had a mean fall and the other a rise in the total cholesterol under sitosterol. A marked difference was encountered in the values before treatment, the mean value in women being 176 mg. as compared with 68·6 mg. per 100 ml. in men.

Total Lipids. During sitosterol administration there was a rise which was statistically significant, mean values of 822·3 mg. before and 913·8 mg. per 100 ml. during sitosterol therapy being obtained from the series.

TABLE II

ANALYSIS OF SERUM LIPID LEVELS OBTAINED BEFORE AND DURING SITOSTEROL THERAPY

	Initial		During therapy		Ratio Difference of means to standard error of the difference	No. of cases
	Mean (mg. %)	Standard deviation (mg. %)	Mean (mg. %)	Standard deviation (mg. %)		
Total cholesterol	304·0	48·7	283·8	49·8	1·48	26
Lipid phosphorus	11·3	1·4	10·5	2·0	1·72	26
Neutral fats	101·7	28·8	221·6	81·7	7·0	26
Total lipids	822·3	163·1	913·8	151·5	2·0	26
Total cholesterol/lipid phosphorus ratio	26·9	4·6	27·3	4·1	Nil	26

Discussion

Sitosterol produced a fall in the serum cholesterol in the series reported in this paper. The results were suggestive rather than significant, and not as great as might have been expected from the reports of Pollack (1953) and Best *et al.* (1954*a*).

The minimum serum cholesterol values during the therapy period were reduced in 24 out of the 26 patients. Pollack showed a fall in this level in 25 out of 26 normal subjects using crude 70 per cent sitosterol from soya bean. The result in the present series might therefore be considered comparable. It was found that considerable fluctuations occurred in most cases, and the present series were analysed on the mean levels obtained during therapy as being a stricter gauge. Under these criteria a fall was only obtained in 17 out of 26 patients, and evaluation of the means of the total sample showed a fall from 303·9 mg. to 283·8 mg. per 100 ml. Best and his co-workers reported on a series of nine patients and found a significant fall in all except one with no escape above the control values.

The diet in this group of patients was unrestricted. This was also so in the two groups discussed above. It is probable that a higher fat content was taken by the American subjects. The dose of sitosterol is probably of great importance and may be the explanation of the poorer results obtained. In this series, 9 g. was given daily, which is equivalent to Pollack's dosage. Since our trial commenced, Best *et al.* published their results using 15–18g., and Joyner and Kuo (1954) found a significant reduction in the serum cholesterol with 12–24 g. and correlated the degree of decrease with the dosage. They considered doses under 10 g. daily to be without effect, although the present series suggests that there is a change, although small.

We have been unable to demonstrate the fall in total lipids and neutral fat reported by other workers (Best *et al.*, 1954*b*). In fact our series shows a rise in calculated neutral fat mainly due to an increase in total lipids. One patient (Case B.15) showed a consistent reduction of serum cholesterol when taking sitosterol but nevertheless died of a further myocardial infarction.

Summary and Conclusions

Beta-sitosterol in dosage of 9 g. daily divided between the three main meals produced a fall in the mean serum total cholesterol which was suggestive, though not significant. It is probable that the dosage required for consistent results is twice this amount.

Biscuits containing this compound were palatable, and no side effects were seen.

One patient who showed a reduced serum cholesterol in response to sitosterol died of a further myocardial infarction.

Since the completion of this paper six more patients have been given 6 g. of sitosterol before meals (18 g. daily). In each instance there has been a rapid and consistent fall in the serum cholesterol.

It is a pleasure to thank the Energen Dietary Service, and their Medical Director, Dr. R. Dixon Firth, for their unfailing co-operation and for the supplies of sitosterol. We are also indebted to Dr. H. F. W. Kirkpatrick of the London Clinic for the laboratory work. Dr. W. H. Moffatt helped us at the City Hospital, Belfast.

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SERUM LIPOPROTEIN PATTERNS IN CORONARY SCLEROSIS AND ASSOCIATED CONDITIONS

BY

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The association of coronary sclerosis with a disturbance of lipid metabolism is now fairly generally recognized. The cholesterol of the atherosclerotic plaque is derived, at least in part, from the circulating cholesterol (Biggs *et al.*, 1952). At present the only objective measure of such a disturbance in the living subject is analysis of the circulating lipids. Previously it has been shown that there is significant elevation in subjects of coronary sclerosis compared with the normal of plasma total cholesterol and its ratio to the total circulating phospholipids, the C/P ratio (Gertler *et al.*, 1950; Steiner *et al.*, 1952; Oliver and Boyd, 1953*b*). There is evidence, which has been summarized by Russ *et al.* (1951), Nikkilä (1953), and Swahn (1953), that the circulating lipids do not exist free in the plasma but are attached to protein. Cholesterol is associated with all the protein fractions but by far the greatest concentration is attached to the α_1 and β_1 globulin fractions (Blix *et al.*, 1941), thus these two lipid-laden globulin fractions are termed the α and β lipoproteins. It is obviously important to study the distribution of cholesterol between these two principal lipid carriers.

An analytical approach towards the estimation of these complex colloidal lipoproteins was only made possible within recent years by the development of new physical methods. The low temperature chemical fractionation of plasma lipoproteins by the elaborate solubility procedure of Cohn *et al.* (1950), even at the micro level as developed by Russ *et al.* (1951), requires about 25 ml. of serum and considerable technical skill. The ultracentrifugal analytical flotation method, which has been so well developed by Gofman *et al.* (1950), for the examination of lipoprotein molecules, necessitates the possession of expensive and complex equipment. A third physical characteristic, the different rate of migration of the protein fractions in a buffer in an electric field, may be utilized for the separation of the lipoproteins by zone electrophoresis. This procedure has been applied with various modifications to the study of lipoproteins by Nikkilä (1953), Swahn (1953), and Rosenberg *et al.* (1954). These authors support the suggestion of Barr *et al.* (1951), that the normal distribution of cholesterol between the two lipoprotein patterns is changed in the presence of coronary sclerosis and that the concentration of cholesterol on the β lipoprotein fraction is increased. The electrophoretic principle is attractive in its simplicity and was therefore employed in this study.

METHOD

The subjects were 50 normal healthy men, 50 men with electrocardiographic confirmation of myocardial infarction, two men and two women with xanthoma tuberosum, one man with xanthoma tendinosum, two men with " essential hyperlipæmia " and one boy with progeria. A study of the younger subjects of coronary disease was regarded as particularly important and thus the majority of this group, whose mean age was 41 years, exhibited hypercholesterolæmia, a very frequent finding at this age (Adlersberg, 1951; Oliver and Boyd, 1953*b*). The control group, which is matched for age, consists of healthy members of university and hospital departments, and in-patients

who had no history or clinical features of atherosclerosis, cardiac, hepatic, metabolic, or renal disease.

Blood samples were not obtained in the fasting state exclusively. None of the subjects of coronary sclerosis were receiving any therapy at the time of the estimation and none had had a myocardial infarct within three months of the determinations, which were repeated on all 50 subjects on several occasions.

The α and β lipoproteins of serum were separated by a filter-paper zone electrophoresis micro technique followed by serial cholesterol estimations. The experimental procedure and method of calculating the $\alpha : \beta$ serum lipoprotein ratio have previously been published (Boyd, 1954). Many serial observations on the same serum sample showed that the accuracy of the $\alpha : \beta$ ratio was ± 3 per cent. The precise details for the estimation of the plasma total cholesterol and plasma lipid phosphorus have been reported previously (Oliver and Boyd, 1953*a*).

Results

The contrast between the serum lipoprotein pattern in the normal with that seen in the presence of coronary sclerosis is shown in Fig. 1, which demonstrates the distribution of cholesterol between the protein fractions. From Table I it can be seen that the percentage of cholesterol attached to the β lipoprotein fraction is 72 in the control group in contrast to 91 in the group of comparable age with coronary sclerosis ($P<0{\cdot}001$), and that there is a decrease in the absolute concentration of α lipoprotein in the latter group. The remainder of the cases listed in Table I are an assortment of subjects who exhibit conditions known to be associated with coronary sclerosis. It is interesting that the concentration of cholesterol attached to the β lipoprotein fraction in these miscellaneous cases closely resembles the pattern observed in established coronary sclerosis. It seemed justifiable to include in this report these few subjects with conditions known to be associated with coronary sclerosis because they are sufficiently rare to restrict much expansion in numbers.

Discussion

These results show that the concentration of cholesterol attached to the β lipoprotein fraction is increased in a group of men with coronary sclerosis when contrasted with a group of normal men of comparable age, and that the concentration of cholesterol attached to the α lipoprotein fraction is correspondingly decreased. It is important to appreciate that the men with coronary sclerosis studied in this report are all comparatively young and thus the majority exhibited hypercholesterolæmia. The increase in the concentration of cholesterol on the β lipoprotein fraction observed in this young group of men with coronary sclerosis was 19 per cent. This compares favourably with an increase of 8 per cent, observed by Barr *et al.* (1951) using his modification of Cohn's fractionation procedure (Cohn *et al.*, 1950), and with an increase of 9 per cent and 12 per cent in the middle-aged groups studied respectively by Nikkilä (1953) and by Rosenberg *et al.* (1954) using filter-paper zone electrophoresis. It is probable that the rather greater increase observed in the present study is largely a function of the hypercholesterolæmia which is so striking in young men with coronary sclerosis, and that, whereas the group can fairly be regarded as representative of the young coronary population, it is probably not a cross-section of the coronary population in general. The elevation of plasma total cholesterol and of the plasma C/P ratio previously observed in coronary sclerosis (Gertler *et al.*, 1950; Steiner *et al.*, 1952; Oliver and Boyd, 1953*b*) is to some extent dependent on this increment of cholesterol on the lipoprotein fraction. The C/P ratio of the β lipoprotein fraction is nearly three times that of the α lipoprotein fraction, and therefore any shift of cholesterol in favour of the β lipoprotein fraction will result in elevation of the overall plasma C/P ratio.

The behaviour of the serum lipoproteins in diffuse atherosclerosis has not been reported so far and thus it cannot yet be said that the patterns described in coronary sclerosis occur also when atherosclerosis predominantly involves the cerebral circulation or the peripheral circulation. It

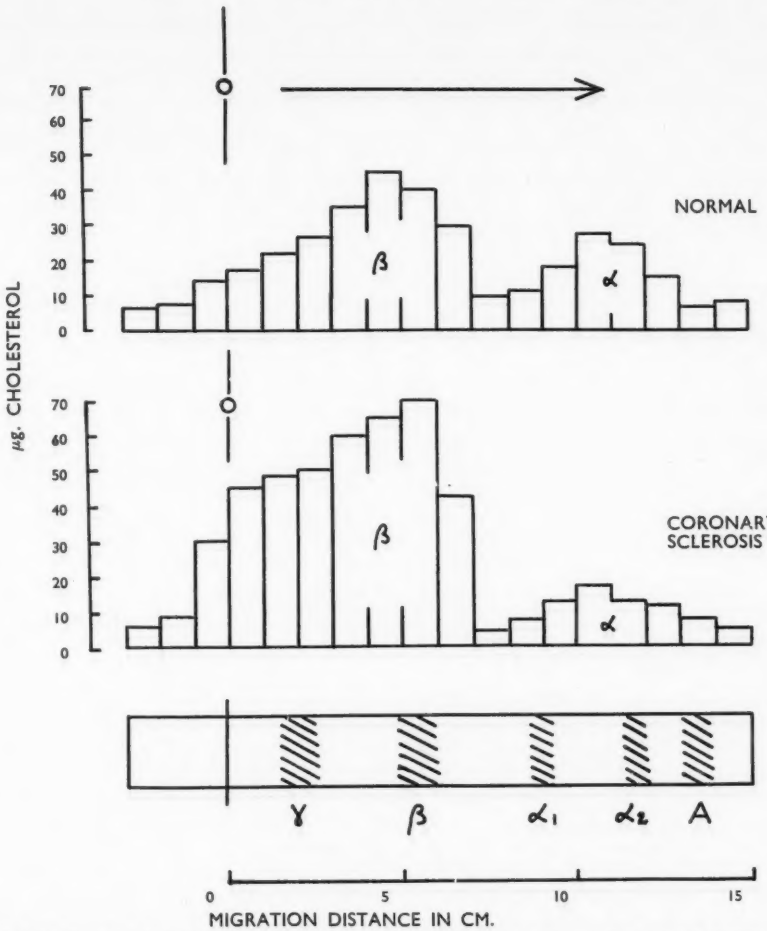

FIG. 1.—The distribution of cholesterol obtained by zone electrophoresis between the α and β lipoproteins in normal healthy men and men with established coronary sclerosis. The arrow indicates the direction of migration of the lipoproteins. The lowest diagram illustrates the protein distribution.

TABLE I

DISTRIBUTION OF CHOLESTEROL BETWEEN THE α AND β LIPOPROTEIN FRACTIONS, EXPRESSED AS THE MEAN α : β RATIO, IN CORONARY SCLEROSIS AND SOME ASSOCIATED CONDITIONS

Subjects	Number of cases	Mean age	Mean α : β ratio	S.D.	Mean plasma total cholesterol (mg%)	Mean C/P ratio
Normal men	50	41	28 : 72	9·8	193	0·82
Men with coronary sclerosis ..	50	41	9 : 91	6·1	270	1·04
Xanthoma tuberosum	4	39	8 : 92	—	371	0·92
Xanthoma tendinosum	1	39	4 : 96	—	420	1·22
"Idiopathic hyperlipæmia" ..	2	37	1 : 99	—	330	1·13
Progeria	1	3	11 : 89	—	235	0·99

is thought that these changes are sufficiently striking to warrant a preliminary communication, and that the electrophoretic separation of lipoproteins may become one of the standard procedures in any future attempt at screening the apparently healthy population and a useful adjuvant towards making the diagnosis of coronary sclerosis before it presents clinically. In our experience so far a very high percentage of patients with established coronary sclerosis have had either an elevated plasma total cholesterol or an elevated plasma C/P ratio or an abnormal distribution of cholesterol between the serum lipoprotein fractions. On the other hand, some clinically healthy subjects have shown these abnormalities but only time will reveal whether they had incipient coronary sclerosis when the observations were made.

Summary

The distribution of cholesterol between the α and β lipoproteins has been determined by zone electrophoresis in 50 men with coronary sclerosis and in 50 healthy men.

The ratio of cholesterol attached to the α lipoprotein fraction to that attached to the β lipoprotein fraction (the $\alpha : \beta$ ratio) has been shown to be significantly lower in the presence of established coronary sclerosis.

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THE EFFECT OF EXERCISE ON LUNG DISTENSIBILITY AND RESPIRATORY WORK IN MITRAL STENOSIS

BY

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The selection of patients with mitral stenosis for valvotomy is considerably influenced by the degree of dyspnœa of which the patient complains, and in many cases the history of progressive dyspnœa with episodes of acute pulmonary œdema or hæmoptysis makes the need for operation obvious. In some cases, however, fatigue is confused with dyspnœa as a reason for limiting physical activity or the symptoms of the effort syndrome may be superimposed so that some objective measurement of the degree of disability might be of value. Attempts to correlate the degree of dyspnœa with the circulatory changes in the heart and lungs, measured by means of the cardiac catheter, or with results of tests of respiratory efficiency have given conflicting results. Most of these studies have been carried out with the patient at rest but even when repeated during steady exercise the same lack of correlation has been reported (West *et al.*, 1953).

Pathologists have long been familiar with the fact that the lungs of patients dying in heart failure were more rigid than normal lungs, but it was not until 1934 that Christie and Meakins (1934) measured *in vivo* the distensibility of the lungs in patients with congestive heart failure by means of simultaneous tracings of the tidal air and the intrapleural pressure fluctuations. They showed that in heart failure the lungs were more rigid than normal, probably because of pulmonary congestion, and that with clinical improvement the distensibility of the lungs improved. There was thought to be a direct relationship between the degree of lung rigidity and the amount of dyspnœa and it was later suggested that cardiac dyspnœa was reflex in origin, the increased lung rigidity through the Hering-Breuer reflex causing the rapid shallow breathing of heart failure (Christie, 1938). Because of the necessity of inducing a small pneumothorax to record the changes in intrapleural pressure little use has been made of the method of Christie and Meakins (1934) of measuring the pulmonary distensibility in cardiac patients. Dornhorst and Leathart (1952) have shown that an accurate record of changes in intrathoracic pressure can be obtained by recording the pressure changes in the œsophagus and this method has been used to study on a larger scale changes in lung distensibility and respiratory work in heart failure (Marshall *et al.*, 1954).

If the degree of cardiac dyspnœa is directly related to the increased rigidity of the lungs, the measurement of pulmonary distensibility might be of help in assessing the amount of disability. In this investigation the relationship between dyspnœa and pulmonary distensibility and respiratory work has been studied in 30 patients with mitral stenosis. Measurements were made at rest, and during and immediately after exercise, and in 6 patients were repeated 3–6 months after mitral valvotomy.

Methods

Changes in intrathoracic pressure were measured using an œsophageal catheter and these were recorded simultaneously with records of the tidal air obtained with the pneumotachograph and capacitance manometer. From these records the distensibility of the lung was calculated and expressed as the pleural pressure change in cm. of water necessary to produce 1000 ml. of tidal

volume change. This is the coefficient of elastic resistance as defined by Marshall *et al.* (1954). In addition the respiratory work was calculated according to the method of Dean and Visscher (1941) and was expressed as kilogram metres/minute. All measurements were made with the patient sitting on a bicycle ergometer. The first record was obtained with the patient at rest, but no attempt was made to have the patients in a basal condition. The patients were then exercised until they were obviously dyspnœic. No attempt was made to standardize the amount of exercise each patient took to reach this point. The patients were then instructed to stop cycling and a third record was taken during the first minute after stopping and while they were still dyspnœic.

The 30 patients with mitral stenosis who were investigated had all been sent to hospital for assessment of their suitability for mitral valvotomy. They were placed in one of the following four grades according to the degree of their dyspnœa.

Grade 1. Dyspnœa after relatively severe exertion.
Grade 2. Dyspnœa on moderate exertion.
Grade 3. Dyspnœa that was severe, with marked limitation of activities and in many cases with a history of cardiac asthma.
Grade 4. Incapacitating dyspnœa with clinical signs of pulmonary congestion and often right-sided heart failure.

Mitral stenosis was judged to be the predominant valve lesion in all cases, although in eight the murmur of aortic incompetence was present.

Results

The distensibility of the lungs as expressed by the coefficient of elastic resistance measured at rest, when dyspnœic during exercise and during the first minute after exercise for the four grades

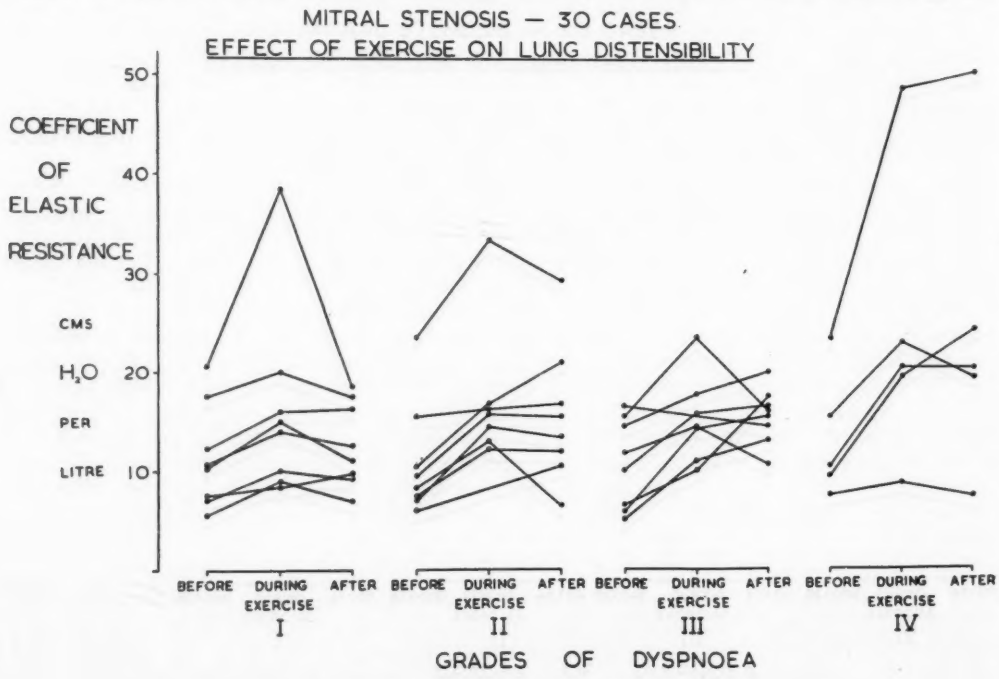

FIG. 1.—The effect of exercise on lung distensibility in 30 patients with mitral stenosis.

TABLE I

THE WORK OF BREATHING AND LUNG DISTENSIBILITY IN 30 PATIENTS WITH MITRAL STENOSIS MEASURED AT REST, DURING AND AFTER EXERCISE

Subject	Age and sex	Grade of dyspnœa	Rest		Exercise			
					During		After	
			Coefficient of elastic resistance (cm. H_2O/l)	Work in kg./m./min.	Coefficient of elastic resistance (cm. H_2O/l)	Work in kg./m./min.	Coefficient of elastic resistance (cm. H_2O/l)	Work in kg./m./min.
E. A.	F. 37	1	5·7	1·31	9·0	1·75	7·1	1·28
M. M.	F. 50	1	7·0	0·42	10·0	1·74	9·4	1·10
W. M.	F. 31	1	7·4	0·68	8·3	2·29	9·6	3·92
A. S.	M. 27	1	10·2	0·59	15·1	5·0	11·4	2·48
H. G.	F. 22	1	10·9	0·59	14·2	2·55	12·5	2·73
M. W.	F. 44	1	12·2	0·65	16·0	1·42	16·2	1·34
E. K.	F. 36	1	17·7	0·8	20·0	0·83	17·7	1·19
N. L.	F. 47	1	20·3	1·02	38·4	2·62	18·7	3·42
A. P.	F. 30	2	8·3	0·71	13·0	1·47	6·4	1·89
A. P.	F. 38	2	6·0	1·14	—	—	10·7	1·53
R. M.	M. 40	2	7·3	1·24	12·3	2·1	12·0	2·80
G. W.	M. 40	2	7·2	1·12	14·7	3·81	13·5	8·05
A. S.	F. 54	2	9·3	0·51	15·7	1·3	15·7	1·35
E. G.	F. 40	2	15·7	0·21	16·2	1·92	16·6	0·68
A. B.	F. 32	2	10·6	0·21	16·9	0·85	21·0	1·28
R. B.	F. 21	2	24·2	1·11	33·4	3·38	29·8	3·60
J. E.	M. 43	3	5·1	0·39	11·4	1·43	13·0	0·82
L. L.	F. 36	3	16·4	0·66	—	—	14·8	1·42
S. V.	F. 36	3	5·6	0·52	14·3	1·67	16·1	1·90
P. F.	F. 42	3	20·4	0·55	23·5	2·81	15·5	1·84
E. H.	F. 39	3	10·6	0·88	15·8	3·94	16·7	2·06
L. W.	F. 27	3	9·9	1·77	10·0	3·3	17·4	3·00
M. S.	F. 20	3	14·5	1·15	17·9	4 3	20·2	2·06
J. A.	F. 38	3	9·95	1·31	13·5	5·07	10·6	2·68
H. W.	M. 44	4	7·3	0·47	8·9	3·0	7·6	1·95
M. H.	F. 22	4	15·2	0·54	23·4	1·9	19·8	2·24
E. A.	M. 30	4	10·4	0·68	20·9	4·83	20·9	2·90
J. H.	F. 26	4	21·6	1·12	—	—	—	—
H. M.	F. 47	4	9·4	0·76	19·4	3·7	24·4	2·50
M. D.	F. 27	4	23·2	0·72	49·0	4·26	50·4	4·54

of dyspnœa is shown in Table I and Fig. 1. The resting distensibility figures show no significant difference in all four grades of dyspnœa. In all cases the lung became more rigid and the distensibility decreased on exercise, but the distensibility when the patient is dyspnœic was approximately the same in those who were assessed clinically as having Grade 1 or Grade 4 dyspnœa. This decreased distensibility on exercise in these patients is in sharp contrast with the increased distensibility on exercise found in normal subjects (Fig. 2). The level of distensibility recorded after exercise was in most cases lower than the level during exercise, but was approximately the same for patients in all four grades of dyspnœa.

Changes in respiratory work at rest, during and after exercise in the four different grades of dyspnœa are shown in Table I and Fig. 3. The work of breathing at rest is within the same range in all four grades (0·21–1·77 kg.m./min·; normal range 0·19–0.46 kg.m./min.) and as previously reported by Marshall *et al.* (1954) increased markedly on exercise. When the patient is dyspnœic the rate of respiratory work is approximately the same whatever the previous

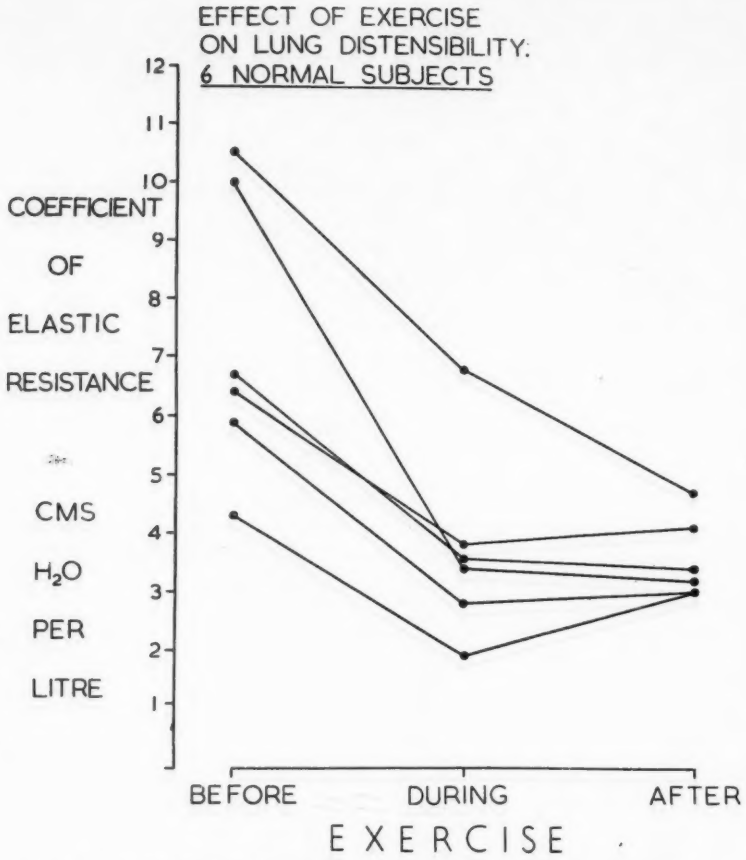

FIG. 2.—The effect of exercise on lung distensibility in 6 normal subjects.

grading of the dyspnœa. As was to be expected from their histories, the most notable difference between the patients was the duration of exercise necessary to produce dyspnœa, a very short period being necessary in Grade 4 whereas patients in Grade 1 could exercise for a much longer period. During the first minute after exercise had stopped, when the patient was often even more conscious of dyspnœa than during exercise, the level of respiratory work has often fallen abruptly.

Six patients were studied again 3–6 months after mitral valvotomy (Table II). Two of them were assessed as having Grade 4 dyspnœa, three Grade 3, and one as having Grade 2 dyspnœa before operation, and all showed a marked improvement in effort tolerance after operation. The mitral valve opening in all cases was small at operation, and in 5 cases a satisfactory increase in the size of the opening was produced. In the sixth case, the cusps could not be split and only a slight dilatation of the opening was possible.

The effects of the operation on lung distensibility are shown in Table II and Fig. 4. The resting distensibility was improved in four of the five successful cases. Before operation, in all cases the

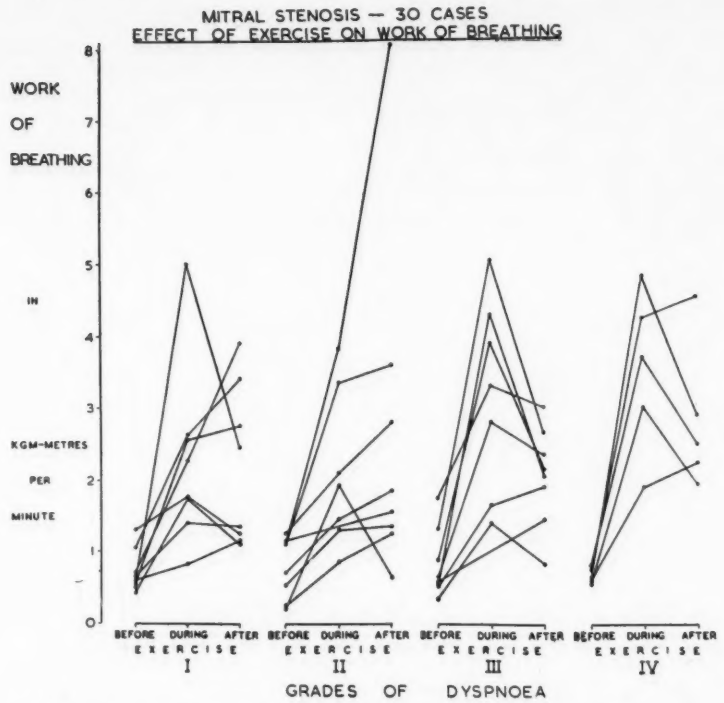

FIG. 3.—The effect of exercise on the work of breathing in 30 patients with mitral stenosis.

TABLE II

THE LUNG DISTENSIBILITY BEFORE AND AFTER MITRAL VALVOTOMY IN SIX PATIENTS

Name		Minute volume (l./min.)			Work (Kg./m./min.)		
		Rest	Exercise		Rest	Exercise	
			During	After		During	After
P. F.	Pre-op.	11·1	23·1	26·0	0·55	2·81	1·84
No. 13	Post-op.	14·9	37·1	28·7	0·57	2·18	1·79
E. H.	Pre-op.	11·8	29·6	25·6	0·88	3·94	2·06
No. 14	Post-op.	10·2	41·5	—	0·46	4·6	—
M. D.	Pre-op.	12·1	15·0	15·3	0·83	1·7	1·4
No. 18	Post-op.	9·8	19·2	21·9	0·58	1·6	2·04
A. P.	Pre-op.	15·6	11·7	23·0	0·71	1·47	1·89
No. 6	Post-op.	11·6	26·6	17·0	0·25	1·46	0·63
J. H.	Pre-op.	17·0	—	—	1·12	—	—
No. 11	Post-op.	9·2	22·5	19·8	0·36	1·72	1·60
L. W.	Pre-op.	18·3	36·4	39·3	1·77	3·3	3·0
No. 15	Post-op.	7·5	14·4	9·5	0·32	1·4	0·68

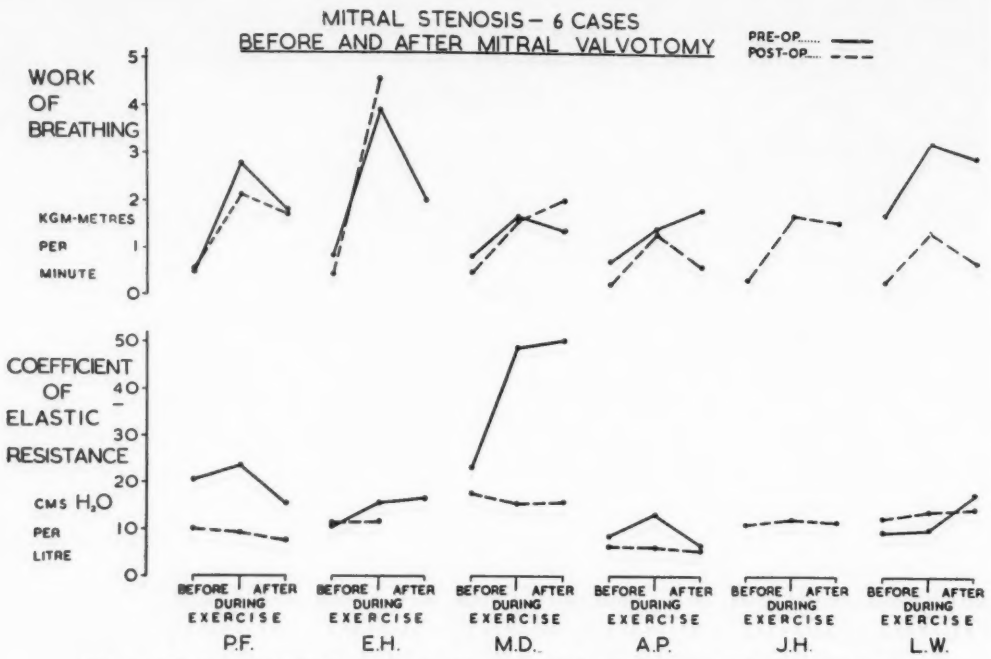

FIG. 4.—The lung distensibility and work of breathing in 6 patients before and after mitral valvotomy.

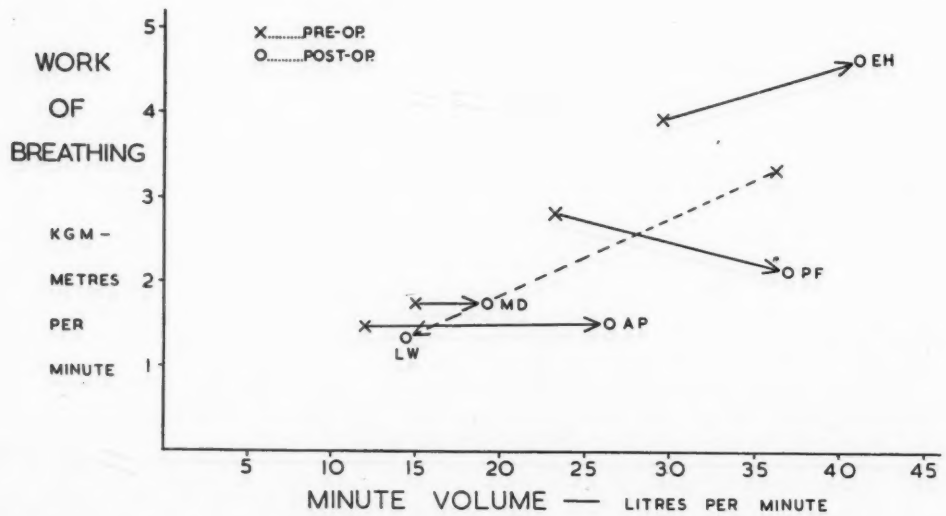

FIG. 5.—The rate of respiratory work and the minute volume when dyspnœic on exertion before and after mitral valvotomy.

lungs became more rigid on exercise and after a successful operation there was no such increase on exercise. In the sixth case (L.W.) no operation on the mitral valve was possible, and although there was marked symptomatic improvement, the lungs at rest were less distensible after the attempted valvotomy. The changes in respiratory work after operation are shown in Table III and Fig. 4. After operation the resting respiratory work was slightly lower in most cases but during exercise sufficient to cause dyspnœa, the rate of work reached the same level as before the operation. The improvement in lung distensibility is well shown by the increased minute volume of respired air after operation associated with a given amount of respiratory work (Fig. 5). In the five cases that had a satisfactory valvotomy the minute volume was increased by from 20 to 125 per cent compared with the preoperative figures, although the rate of respiratory work at the point of dyspnœa was unchanged.

TABLE III

THE WORK OF BREATHING AND MINUTE VOLUME IN SIX PATIENTS BEFORE AND AFTER MITRAL VALVOTOMY

Name, sex, age		Grade of dyspnœa	C/T ratio	Pulmonary artery mean pressures in mm./Hg		Lung distensibility (Cm. of H_2O/l. of airflow)			Operation data
						Exercise			
				Rest	Exercise	Before	During	After	
P. F. F. 42 No. 13	Pre-op. Post-op.	3 1	12·5/25 —	34 —	50 —	20·4 10·1	23·5 9·3	15·5 7·2	Valve 1·5×0·5 cm. Admits 2 fingers
E. H. F. 39 No. 14	Pre-op. Post-op.	3 1	14·3/26·5 —	50 —	73 —	10·6 11·2	15·8 11·7	16·7 —	Valve 1·0×0·5 cm. Admits 1½ fingers
M. D. F. 27 No. 18	Pre-op. Post-op.	4 0	15·0/25 —	— —	— —	23·2 17·8	49 15·3	50·4 15·8	Valve 1·0×0·5 cm. Admits 2 fingers
A. P. F. 30 No. 6	Pre-op. Post-op.	2 0	12·5/28 —	27 —	41 —	8·3 6·5	13·0 6·2	6·4 5·8	Valve 1·5×0·5 cm. Admits 1½ fingers
J. H. F. 26 No. 11	Pre-op. Post-op.	4 0	13·0/25 —	58 —	68 —	15·6 11·4	— 12·0	— 11·6	Valve 1·0×0·5 cm. Admits 1 finger
L. W. F. 27 No. 15	Pre-op. Post-op.	3 1	14·8/26 —	26	36	9·9 12·6	10·0 13·8	17·4 14·1	Valve 1·5×0·5 cm. Dilated— Not possible to split

DISCUSSION

The results reported here confirm earlier reports on the increased rigidity of the lung in mitral stenosis. The cause of the increased rigidity is generally assumed to be chronic passive congestion of the pulmonary capillary circulation although it seems probable that interstitial and alveolar œdema is of greater importance in making the lung rigid. Hayward and Knott (1954) by perfusion of the isolated animal lung have shown that although either increased pressure in the pulmonary arteries or capillary congestion cause a slight decrease in lung distensibility the effect is small compared with the changes occurring when there is œdema of the lung. Hæmodynamic studies, using the cardiac catheter, of the circulatory changes in the lungs in patients with mitral stenosis lend support to this view. The pulmonary capillary venous pressure, measured by impacting the catheter tip in a pulmonary arteriole, is normal or slightly raised at rest and during exercise rises

appreciably, frequently to a level exceeding the plasma osmotic pressure of 30 mm. Hg (Gorlin *et al.*, 1951). Clinical pulmonary œdema does not necessarily occur when the pulmonary capillary pressure exceeds the plasma osmotic pressure. The thickening of the alveolar and capillary walls and changes in the interstitial tissue (Parker and Weiss, 1936) may hinder the transudation of fluid from the capillaries, and as Drinker (1945) has shown, œdema fluid only appears in the air passages when the pulmonary lymphatics are unable to remove fluid from the interstitial tissues as fast as it escapes from the capillaries. The greatest increase in lung rigidity in the whole series occurred in the one patient in Group 4 who had obvious clinical signs of pulmonary œdema and was grossly dyspnœic. In all the other cases it is probable that the increased rigidity was due to interstitial œdema and capillary congestion, and catheter studies in these showed a pulmonary capillary pressure on exercise exceeding the plasma osmotic pressure. The effect of mitral valvotomy on the pulmonary circulation is to lower the left auricular, pulmonary capillary, and pulmonary arterial pressure, measured at rest, and to abolish or decrease the rise in pressure that occurs on exercise (Munnell and Lam, 1951). These changes are reflected in the measurements of pulmonary distensibility before and after a successful valvotomy which has relieved pulmonary congestion. The striking increase in rigidity (and decreased distensibility) which occurs on exercise before operation is abolished by a valvotomy, the lung after operation behaving as does the normal lung on exercise.

It is clear from the results of this investigation that the measurements of lung rigidity and respiratory work cannot be used as an objective measurement of dyspnœa or as a means of selecting patients for valvotomy when the degree of disability is uncertain from the history. The lack of any significant difference between the rigidity of the lungs in patients of any grade of disability who were made dyspnœic by exercise and the fact that after a successful valvotomy dyspnœa occurs with no increase in lung rigidity shows that the severity of dyspnœa cannot be directly related to the increased rigidity of the lungs in mitral stenosis.

The increased rigidity of the lung is responsible for the high rate of respiratory work which occurs on exercise and also for the low minute volume of respired air in spite of a considerable increase in the extent of the intrathoracic pressure variation on exercise. After valvotomy, when the lung does not become more rigid on exercise, the same amount of respiratory work produces a minute volume that is increased by from 20 to 125 per cent of the preoperative figures.

The rate of respiratory work increases very considerably on exercise in all these patients with mitral stenosis (0·8 kg.m./min. to 5 kg. m./min) but when dyspnœic it falls within the same range whether the patient's disability had been classified as Grade 1 or Grade 4. The chief difference between the patients was the total duration of exercise they were able to carry out before becoming dyspnœic, and the method of exercise used does not enable the total amount of work to be calculated.

Although there is no relationship between dyspnœa and the rate of respiratory work, the considerable increase that occurs on exercise is of interest as the ability to carry out muscular (and respiratory) work efficiently is closely related to the degree of disability. Studies on the mechanical efficiency of cardiac patients in carrying out muscular work show that patients with a normal or only slightly decreased effort tolerance are able to carry out light or moderate work with normal efficiency, whereas those with severe incapacity show a marked decrease in muscular efficiency (Simonson and Enzer, 1942). The decrease in efficiency runs parallel with the inability to increase the stroke volume of the heart. In the patients with severe mitral stenosis and Grade 4 disability, the circulatory adjustments that lead to efficiency in carrying out muscular work are all impaired. The cardiac output at rest is low and on exercise frequently fails to increase and may actually fall. The oxygen extraction (A-V difference) at rest is high and, as the oxygen uptake cannot be increased on exercise, the increased oxygen for the muscles can only be supplied by increasing still further the A-V oxygen difference. Lack of training, poor muscular development due to enforced inactivity, and the early onset of fatigue are other factors that decrease the efficiency of muscular performance in these patients. All these factors lead to inefficient performance of muscular work including

respiratory work, and may be partly responsible for the decreased effort tolerance which is one of the chief indications for a mitral valvotomy.

The effect of psychological factors on the onset of dyspnœa is well recognized. In the patient L.W. (Table II and Fig. 4) and in five other patients in whom it has been technically impossible to carry out a valvotomy after thoracotomy, there has been a remarkable immediate improvement in the patient's dyspnœa after operation. L.W. in her assessment after the attempted operation had improved from Grade 3 to Grade 1 despite the fact that her lungs were less distensible than before the operation. This subjective improvement was real and although it may only be temporary, illustrates the way in which psychological factors may influence effort tolerance.

Summary

In mitral stenosis, the distensibility of the lungs may be decreased at rest and become further decreased on exercise as the result of pulmonary congestion and interstitial and alveolar œdema. The increase in respiratory work on exercise is many times greater than that found in the normal person. After a successful mitral valvotomy the lung behaves as does the normal lung on exercise and no decrease in distensibility occurs. The improvement in distensibility of the lung as a result of the lowering of left atrial, pulmonary capillary, and pulmonary artery pressures by mitral valvotomy is shown by the considerable increase in the minute volume of respired air which the same amount of respiratory work produces after operation. There is no relationship between the degree of dyspnœa and the rigidity of the lung, and measurements of lung distensibility when patients of all grades of disability were exercised to make them dyspnœic fell within the same range. The decreased muscular efficiency of patients with mitral stenosis may be partly responsible for their decreased effort tolerance.

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PULMONARY HYPERTENSION ASSOCIATED WITH NECROTIZING PULMONARY ARTERITIS

BY

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Necrotizing arteritis limited to the pulmonary arteries has been described occasionally as a complication of mitral stenosis (Parker and Weiss, 1936), of Eisenmenger's complex (Old and Russell, 1947), and in patients dying with right heart failure of uncertain causation (McKeown, 1952). One such case in this last category, in which cardiac catheterization gave clear evidence of pulmonary hypertension, has recently come under our observation.

Case Report

The patient, a boy of 13, was admitted to the Royal Infirmary, Aberdeen, in June, 1951, with chorea. He had previously suffered from measles, mumps, chicken pox and whooping cough. For a short time in 1949, and again in 1950, he had complained of mild pains in his thighs. Seven weeks before admission to hospital he developed a sore throat, followed in three weeks by severe pains in his legs. His doctor noted pyrexia and confined him to bed. After a fortnight, symptoms and signs of chorea appeared and a week later his right wrist became painful and swollen. Mild epistaxis occurred on two occasions.

Examination showed an intelligent, obese boy with frank chorea. There was a fading erythema on the upper trunk. Clinically, the heart was not enlarged. A soft systolic murmur was heard at the apex. The pulse rate was 100 and blood pressure 130/90. Hæmoglobin was 12·4 g. per 100 ml., white cell count 9,300 per c.mm., and E.S.R. 54 mm. in one hour (Westergren). An electrocardiogram on 19/6/51 showed no definite abnormality (Fig. 1). But for the appearance of an erythematous rash, which, it was thought, might be due to sensitivity to phenobarbitone, the course of his illness was uneventful. The rash cleared up rapidly following treatment with " anthisan " (mepyramine maleate) 50 mg. b.d. The only abnormal finding when he left hospital on 30/7/51 was the apical systolic murmur.

This was noted again when he was seen as an out-patient in September, 1951. He returned to school then, three months after his admission to hospital. He remained well until February, 1952, when he developed what seemed to be an upper respiratory tract infection, followed by bronchitis. After this he became unduly breathless and tired on exertion. No cyanosis was observed. He was readmitted to hospital, because of these symptoms, in June, 1952. The only abnormal physical finding was the soft apical systolic murmur. The sedimentation rate was now 12 mm. in one hour and the sleeping pulse 75–85. X-ray of the chest showed an increase in the transverse diameter of the heart (cardio-thoracic ration 0·6:1) and prominence of the pulmonary artery segment. The branches of the pulmonary artery were, if anything, less obvious than normal. The electrocardiogram showed a gross change from the first tracing (Fig. 1). There was marked right axis deviation : in lead VI the R wave measured 8 mm. and the S wave had disappeared. In lead aVR, R:S ratio was 4–5 and the T waves were inverted in leads II, III, aVF, VI, V3, and V5. The changes clearly indicated marked right ventricular hypertrophy and strain, which had developed within the previous year. He made no complaint while in the ward and was discharged home in August, 1952.

He was readmitted in November. After feeling vaguely unwell for three days, he had developed extreme breathlessness at rest, associated with a rigor and cyanosis. The dyspnœa passed off in about an hour but the cyanosis lasted somewhat longer. On admission two hours later, his colour was normal and he was free of symptoms. Physical examination showed a diffuse apex beat. Right ventricular pulsation

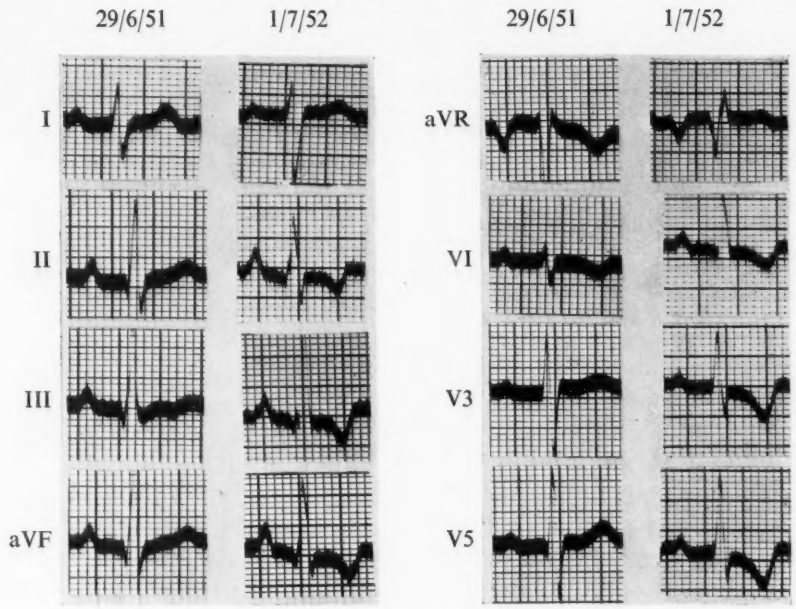

FIG. 1.—Electrocardiograms on 29/6/51 and 1/7/52, showing development of signs of right ventricular hypertrophy during this year.

could now be felt easily in the third and fourth intercostal spaces, and there was a diastolic thrill and murmur in the second and third interspaces, at the left sternal border. The systolic murmur was still present at the apex. The white cell count was 8600 per c.mm., E.S.R. 7 mm. in one hour and Hb. 13·6 g. per 100 ml. An electrocardiogram showed no significant change from that of July, 1952. The only new finding on X-ray screening of the heart was very vigorous pulsation in the enlarged pulmonary artery. There were no further developments while he was in the ward and he was discharged in December, 1952.

On January 2, 1953, he was readmitted for cardiac catheterization. The physical findings had not changed. E.S.R. was 2 mm. in one hour; Hb. 14 g. per 100 ml. Cardiac catheterization was unusually difficult. Despite prolonged and repeated attempts the pulmonary artery could not be entered. The mean right ventricular pressure was grossly elevated (60 mm. Hg above a plane 5 cm. behind the manubrium sterni; normal, approximately 10 mm. Hg). The right atrial pressure was 12 mm. Hg (normal 5 mm. Hg). There was no significant variation in the oxygen content of samples of blood from the superior vena cava, the righ atrium and the right ventricle. Unfortunately an arterial sample was not obtained. Just after the catheterization was terminated the boy became cyanosed and his pulse rose to 130. He lost consciousness momentarily on three occasions in quick succession. An electrocardiogram taken soon afterwards showed sinus tachycardia but no other new abnormality. He was drowsy throughout the remainder of the day but made no specific complaint and next day was back to his usual state. He went home on January 16. At this time there was clinical, cardiographic and radiological evidence of right ventricular hypertrophy. Pulmonary hypertension could be inferred from the findings on cardiac catheterization. The diastolic murmur was thought to be due to pulmonary incompetence.

On January 30, he was readmitted to the ward. During the previous few days he had become increasingly tired, weak and deeply cyanosed on the slightest exertion. He had vomited on several occasions. When he was seen in hospital varying cyanosis and signs of right ventricular failure were evident. There was no change in the cardiac murmurs. Despite treatment with digitalis and mercurial diuretics and the intermittent use of oxygen, he became steadily worse and died on February 4, 1953. Shortly before death the pulmonary diastolic murmur disappeared.

Post-mortem Findings. Post-mortem examination showed hypertrophy and dilatation of the right heart and long-standing chronic venous congestion, evidenced by an advanced " nut-meg " condition of the liver, large pleural effusions and ascites.

The heart weighed 450 g., compared with a normal weight of 216 g. at this age (Vierordt, 1906). This increase in weight was almost wholly due to the great hypertrophy of the wall of the right ventricle, which was 10 mm. across at its thickest part (normal 2·5–3 mm.). The trabeculæ and papillary muscles were very prominent, and there was a notable hypertrophy of the infundibulo-ventricular crest. There was no abnormality of the tricuspid or pulmonary valves. A few flecks of atheroma were evident in the pulmonary trunk. The left side of the heart was normal. The lungs were greatly collapsed. The trachea and main bronchi contained blood-stained muco-pus. A small infarct was noted at the base of the right upper lobe with recently formed thrombus in the related artery. No other macroscopic abnormality was noted. A search was made for thrombus formation in the systemic veins but none was found. The kidneys together weighed 280 g. They were firm and congested. Stripping of the capsules left a smooth surface. The spleen and gastrointestinal tract showed notable congestion.

Histological Report

Heart. Foci of perivascular and subendocardial fibrosis were seen in the sections, associated with a sparse collection of mononuclear cells but nowhere was there a cellular aggregate identifiable as an Aschoff body, in three blocks taken from right and left ventricle.

Aorta and Pulmonary Trunk. There was no evidence of an aortitis or of arteritis in the main pulmonary trunk.

Kidneys. Many of the glomerular tufts were digitate and more cellular than normal, due to an increase in endothelial cells. Adhesions between tuft and Bowman's capsule were not infrequent. A very occasional sclerosed glomerulus could be identified. There were no notable changes in the tubules and renal vessels; in particular, there was no evidence of necrotizing arteritis or arteriolitis.

Lungs. Serial sections from nineteen blocks of tissue from different portions of lung were examined by hæmotoxylin and eosin, by Verhoeff's method for elastic tissue and by Masson's trichrome stain. In each section examined the great majority of the arterioles and small arteries showed some gross abnormality. In a small number of arteries an acute necrotizing lesion was seen. This varied from a zone of subendothelial fibrinoid necrosis to a lesion involving the whole wall, characterized by necrosis of the media and a heavy infiltration of all coats by neutrophil polymorphonuclear leucocytes and mononuclear cells (Fig 2 and 3); neither eosinophil leucocytes nor giant cells were identified. The majority of the vessels showed hypertrophy of the media and gross fibro-cellular thickening of the intima, without leucocytic infiltration. The lumen in these arteries was either greatly reduced or absent (Fig. 4). That this lesion could be remarkably localized is seen in a longitudinal section of artery in which a plaque of thickened intima on one segment of its wall almost occluded the lumen (Fig. 5). A number of extensively damaged arteries were observed, in which the processes of organization and recanalization were active (Fig. 6). Clumps of amorphous hyaline material were often seen in the walls of these recanalized vessels.

In addition to the arterial changes, an acute hæmorrhagic bronchitis was noted, accompanied by focal hæmorrhage and œdema in the related lung parenchyma.

Comment on Pathological Findings

Heart. The microscopical features were not diagnostic of a rheumatic lesion, but they are regarded as constituting evidence of an old myocarditis, which might well have been rheumatic.

The difficulty encountered in attempting to pass the cardiac catheter from the right ventricle into the pulmonary trunk may be explained by the hypertrophy of the infundibulo-ventricular crest which projected into the ventricular cavity.

Kidneys. The changes in the kidneys are not regarded as inflammatory in origin and are attributed mainly to the effects of prolonged and severe chronic venous congestion.

Lungs. The right ventricular hypertrophy, atheroma of the larger pulmonary arteries, and medial hypertrophy in the pulmonary arterial tree, are evidence of pulmonary hypertension. The possible significance of the necrotizing arteritis is discussed below.

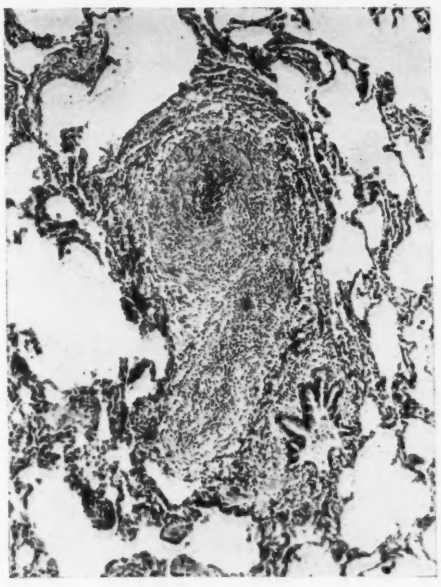

FIG. 2

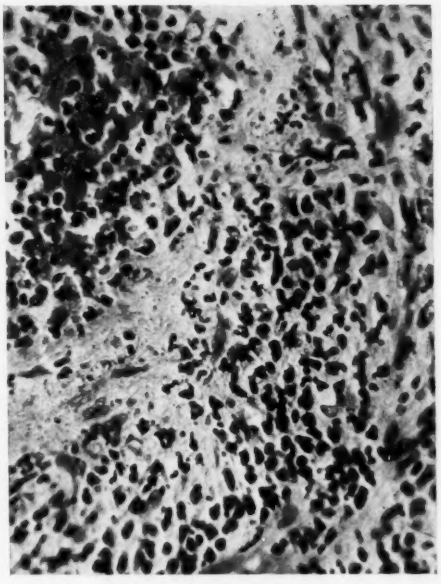

FIG. 3

FIG. 2.—Small pulmonary artery, showing medial necrosis and cellular infiltration of whole wall (× 70).

FIG. 3.—High-power view of Fig. 2, showing neutrophil polymorphonuclear leucocytes and mononuclear cells in the wall of the artery (× 280).

FIG. 4.—Pulmonary artery almost occluded by intimal thickening (× 70).

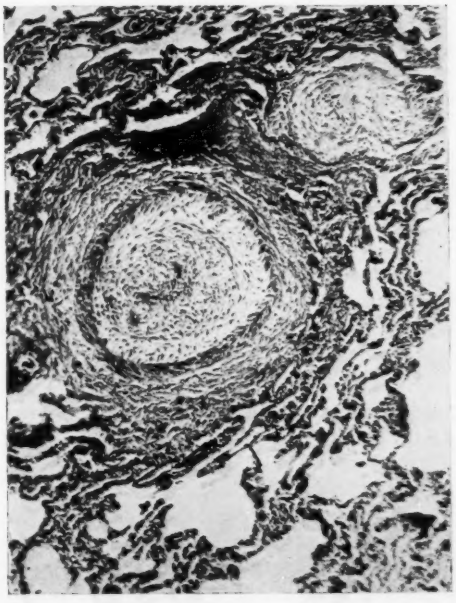

FIG 4

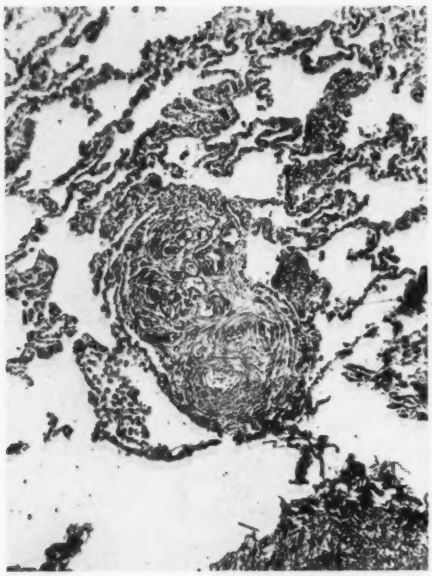

FIG. 5.—Pulmonary artery, showing localized focus of intimal fibrosis (× 90).

FIG. 6.—Recanalization of small pulmonary artery (× 70).

DISCUSSION

Although direct measurement of the blood pressure in the pulmonary artery was not achieved in this case, the gross elevation of the mean pressure in the right ventricle, in the absence of any lesion such as pulmonary stenosis, leaves little or no doubt that there was considerable hypertension. Furthermore, the electrocardiographic evidence shows that right ventricular hypertrophy had been detectable more than seven months and less than nineteen months before death (Fig. 1). There was no mitral stenosis or congenital cardiac defect to account for the hypertension and hence the case must be considered either as one of idiopathic pulmonary hypertension with subsequent acute arterial changes or as hypertension secondary to necrotizing arteritis. The latter possibility will be considered first.

Primary Arterial Disease. It is well established that right ventricular hypertrophy and, by inference, pulmonary hypertension can be caused by an obliterative disease of the pulmonary arteries as in bilharzial disease of the lungs (Shaw and Ghareeb, 1938; Bedford *et al.*, 1946) and in carcinomatosis associated with invasion and blockage of the vessels (Morgan, 1949). In our case, the diagnosis of rheumatic arteritis must be considered. The patient had a history of chorea, leg pains, and at least one swollen joint about 19 months before death. At necropsy there was no evidence of an endocarditis but there were the non-specific features of a healed myocarditis, which might have been rheumatic in origin. Against a diagnosis of primary rheumatic arteritis the following histological evidence can be adduced. (1) Most of the lesions in the pulmonary arteries are much more recent than the known period of right ventricular hypertrophy. (2) If the whole syndrome had been due to a smouldering rheumatic process in the pulmonary arteries, it would be most unusual, indeed, to find it confined to these vessels while no active lesions are demonstrable in heart, aorta, or pulmonary trunk (Gross, 1935). According to Friedberg (1949), cor pulmonale, secondary to rheumatic pulmonary arteritis, has never been proven.

The lesions observed in the pulmonary arteries could be interpreted as polyarteritis nodosa or as a manifestation of allergy. That such a picture can result from allergy has been shown experimentally by Rich and Gregory (1943), who established in rabbits a condition similar to serum sickness in man. In this boy a rash developed during the exhibition of phenobarbitone at the time of his chorea, and some effect on his pulmonary arteries could be postulated. The recent character of most of the arterial lesions makes it unlikely that such a process initiated the pulmonary hypertension.

Idiopathic Pulmonary Hypertension. Idiopathic hypertension in the pulmonary arteries, evidenced by otherwise unexplained hypertrophy of the right ventricle, has been described when no significant structural changes could be demonstrated in the arteries (East, 1940; Armstrong, 1940). In at least one case (Whittenberg, 1950) pulmonary hypertension has been proved by cardiac catheterization, and subsequent post-mortem examination showed only minimal changes in the vessels. It has been estimated (Dresdale *et al.*, 1951) that about half of the cases show occlusive lesions of the smaller arteries and arterioles.

Necrotizing pulmonary arteritis has been described in a case of idiopathic pulmonary hypertension (Symmers, 1952). McKeown (1952) described similar changes in four cases of right ventricular failure of unknown ætiology. It has been recorded in the pulmonary hypertension of Eisenmenger's complex (Old and Russell, 1947; Kipkie and Johnson, 1951). It has been found where pulmonary hypertension has occurred from mitral stenosis (Parker and Weiss, 1936; Symmers, 1952; Hicks, 1953). Conflicting conclusions have been drawn by these authors about the cause of the lesions Polyarteritis nodosa, hypersensitivity reaction, and rheumatism have all been suggested. Pulmonary hypertension seems to be the only factor common to the clinical conditions described, and Symmers' (1952) suggestion that the necrotizing arteritis is the result of pulmonary hypertension seems the best explanation. He compared the changes to those of systemic hypertension in its malignant phase.

In our case, right ventricular hypertrophy was well established seven months before death and therefore pulmonary hypertension must have been present for an even longer period. There is little doubt that the majority of the arterial changes were much more recent and accordingly we regard our case as one of idiopathic pulmonary hypertension with subsequent necrotizing arteritis. The arterial changes are of such severity and so widespread that they must, by obstructing the pulmonary arterial branches, have caused further increase in pulmonary artery pressure, so producing a vicious circle and what might be termed a " malignant " termination.

The cause of the initial rise in pulmonary artery pressure is unknown. Anoxia has been shown to cause pulmonary hypertension experimentally (von Euler and Liljestrand, 1946) and it is thought to be the main cause of cor pulmonale in chronic pulmonary emphysema (Harvey *et al.*, 1951). It is worthy of note that cyanosis appeared late in the course of the illness, in our case, and that even three weeks before death there was no evidence of polycythæmia to suggest long standing arterial anoxia.

Summary

A case of pulmonary hypertension and necrotizing pulmonary arteritis is described.

Serial electrocardiograms allowed some assessment of the rate of development of the hypertrophy of the right ventricle and, indirectly, of the pulmonary hypertension.

The relationship between the hypertension and arteritis is discussed, and the concept of a " malignant " ending to an idiopathic pulmonary hypertension is favoured.

Cardiac catheterization was unusually difficult to perform and was followed by syncopal attacks.

Cyanosis appeared late in the illness and there was no evidence of polycythæmia to suggest long standing arterial anoxia.

We are greatly indebted to Dr. R. J. Duthie for permission to publish this case, and to Professor J. S. Young and Dr. Duthie for helpful advice and criticism. We wish to thank Mr. R. Drummond for the photographs and Mr. N. Mowat for technical help.

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AGE AND SEX FACTORS IN CORONARY ARTERY DISEASE

BY

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Age and sex have hitherto received less consideration than they merit in publications dealing with prognosis and mortality in coronary artery disease. Yet a clear knowledge of all factors that influence mortality is of paramount importance at a time when the efficicacy of modern methods of treatment is under critical review. Even in the matter of their influence on ætiology, age and sex have received less prominence than the facts would seem to justify.

It is common knowledge that coronary artery disease is much more frequent in men than women: estimates have varied between seven to one (Mackenzie, 1923) and four to one (Block *et al.*, 1952). It is also widely recognized that coronary artery disease reaches its maximum incidence in the fifth, sixth, and seventh decades of life. Nevertheless few references can be found to the striking difference between the age incidence in males and that in females. Block *et al.* (1952) hint at the existence of such a difference when they state that the preponderance of men becomes less in the older age groups. Johnston (1954) thinks the age incidence is about ten years later in women than in men.

Mortality figures are usually quoted for entire groups of patients comprising both sexes and all ages, as though the mortality were not appreciably affected by age or sex. Yet, without actually saying so, Mackenzie (1923) implies that the disease is more rapidly fatal in the elderly than in the young when he writes (p. 138) " If we put aside *the relatively few patients in whom death occurred before* 50 *years of age* we will find that the deaths follow closely that of the general death rate " (my italics). Of his 214 patients whose age at death is given (p. 118), 24 were aged under 50; the largest number of deaths occurred in the quinquennium 61–65 (p. 116). The figures of Block *et al.* (1952) show a steadily diminishing percentage of survivors, both at five and at ten years after onset, as the age at onset advances from under 40 to over 80. Cole *et al.* (1954) quote figures that show a later incidence in women than men, a steadily rising mortality in men as age increases, a relatively higher mortality in women than in men of the lower age groups, and a considerably smaller rise in mortality with increasing age in women.

Material and Methods

The investigations, in the course of which the present observations were made, were originally begun for a different purpose, namely to assess the immediate and remote prognosis in patients who have had what may be termed an " acute coronary episode." The material therefore includes patients who have experienced such an episode—an attack of cardiac infarction, an attack of angina pectoris (" acute coronary insufficiency " or " acute cardiac ischæmia "), abrupt onset of effort angina, or abrupt change in the severity or behaviour of pre-existing effort angina. It does not include cases of chronic angina of effort which have started so insidiously and progressed so slowly that no definite " episode " could be recognized. The patients were seen in consulting practice from 1930 up till the end of 1953, and the material therefore covers a wider range of severity than series based on hospital admissions. Analogous cases referred to the outpatient department or admitted to the cardiac wards of the Victoria Infirmary, Glasgow, between January, 1951, and December, 1953, have also been studied.

For purposes of age and sex incidence, the entire group has been used. For purposes of mortality and survival records, only the 1930–50 consulting practice cases are used. These form a " pre-anticoagulant " series of cases, intended as a yardstick for comparison in due course with corresponding figures from 1951 onwards, this being the time when treatment of selected cases by anticoagulants was begun on a large scale. Prior to 1950, only four patients in the entire series received anticoagulant treatment. Twelve patients treated with anticoagulants in 1950 have been excluded from the series.

A diagnosis of *cardiac infarction* has been based on either (*a*) characteristic changes in the QRS complex of the cardiogram; (*b*) changes confined to RT and T if accompanied by pericardial friction, fever, or leucocytosis, or if followed by embolism; (*c*) in the absence of a cardiogram, a typical clinical picture if followed by embolism or confirmed by necropsy. A diagnosis of *cardiac ischæmia* has been made when cardiographic changes have been confined to RT or T and have not been followed by one or other of the signs mentioned in (*b*) above. Cardiac ischæmia has also been accepted as a diagnosis when typical coronary pain has occurred either at rest or on effort, even though the cardiogram has been normal after the pain has subsided.

The immediate mortality and short-term prognosis (up to six weeks) have been assessed in relation to " attacks "; that is to say, a patient who takes a second attack a few months or years after apparent recovery from the first one, is included for this purpose on both occasions. Long-term survival has been assessed in relation to single patients irrespective of the number of attacks each may have experienced: each patient is included once only, and the survival period is given from the date of the first attack.

Survivors are included in the tables for the number of years they are known to have survived; likewise, deaths are included only for the number of years they have been dead. Thus the figures for deaths and survivors at five years includes all patients seen up to and including 1949 while the ten-year figure includes those seen up to the end of 1944. They are based on the information available up to December 31, 1954.

Discussion

Age and Sex Incidence. The overall proportion of males to females was four to one. However this ratio varies in different age groups. The youngest male was aged 28, and there were several between this age and 43 which was the age of the youngest female. Below age 50 the ratio of males to females was seven to one; between 50 and 59 it was almost ten to one. From 60 to 69 the ratio had dropped to just over four to one, while from 70 onwards it was under two to one.

In males the incidence remains very low up to the age of 40 when it begins to rise steeply, reaching a high peak in the age group 55–59; thereafter it falls almost as steeply as it rose (Fig. 1). In females on the other hand, the rise in incidence is slow but steady, almost in a straight line from age 40 to 70. It seemed possible that these findings might be due to the composition of the population at risk, females outnumbering males in the higher age groups. Population statistics were therefore obtained from the Registrar-General for Scotland, and in Fig. 2 the number of cases in each age-sex group has been adjusted upwards or downwards to make it " per 100,000 persons living " of that sex and in that age group. Far from abolishing the sex differences, this has only served to emphasize them. The female incidence approaches even more closely to a straight line. The low incidence in males under 40 becomes more striking, the ascending limb of the incidence curve is smoothed out, the peak at age 55–59 persists, and the striking fall after that age remains.

It is clear that these differences in incidence must imply different ætiological factors affecting the two sexes. The female incidence is what might be expected in a disease associated with the processes of ageing. In this case some additional factor must be present in males aged 40–59 to produce the rapidly rising incidence, and must cease to operate at or about age 60 to account for the diminishing incidence above that age. It might be tempting to blame occupational factors if the peak occurred at age 65; but if occupation were responsible it is difficult to see why the incidence should be falling steeply during the five years before the common retiring age, at the very time when the effects of lifelong occupation might be expected to be exerting their maximal influence. An alternative hypothesis was put forward by Oliver (1954) in a dis-

cussion at the Glasgow meeting of the British Medical Association; he suggested that in females an inhibitory factor may be present during the sexually active period of life. This could account for the extremely low incidence in younger women, and for the later rise in that sex; but it could not explain the steep fall in males after the age of 60, a fall that occurs while the female incidence is still rising.

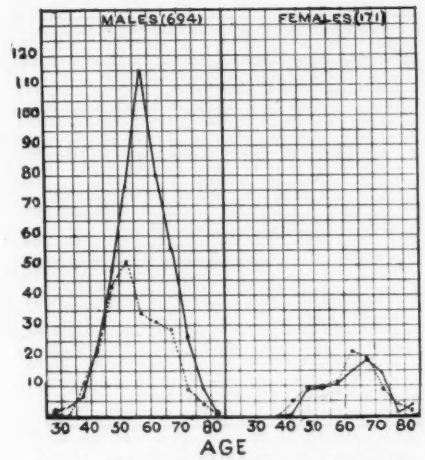

FIG. 1.—Age and sex incidence of coronary attacks. Cardiac infarction •—•. Ischæmia without infarction. ○·····○.

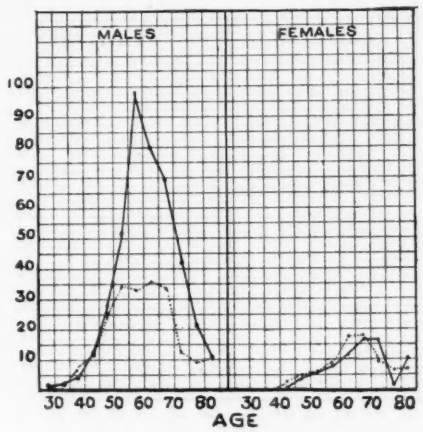

FIG. 2.—Age and sex incidence of coronary attacks, adjusted to correspond to 100,000 living in each quinquennium. Cardiac infarction •—•. Ischæmia without infarction. ○·····○.

Cardiac Infarction and Cardiac Ischæmia. A second interesting difference between the sexes, also shown in Fig. 1 and 2, is in the ratio between attacks with (continuous line) and without (dotted line) infarction. In females attacks with and without infarction are almost equal in number at all ages; the continuous and dotted lines follow one another closely. Thus half the " coronary episodes " in women are associated with infarction while no infarction occurs in the remaining half. In males the same state of affairs is found up to age 50; but once this age is passed infarction becomes much more frequent. Three-quarters of the " coronary episodes " in males over 50 result in infarction.

It is becoming increasingly recognized that " coronary occlusion " and " cardiac infarction " are not interchangeable terms. Snow *et al.* (1952) mention three hearts in which a single occlusion gave rise to two anatomically separate infarcts. Conversely, Blumgart *et al.* (1940) found 53 main vessel occlusions with only 16 infarcts in a series of 30 hearts; while Ravin and Geever (1946) examined at necropsy 166 unselected hearts of which 13 showed occlusion without infarction. Papp and Shirley Smith (1951) postulate coronary occlusion resulting in multiple small areas of necrosis as one possible basis for what they call " slight coronary attacks ": signs of gross infarction are absent; the end result may be small intramural scars, and the cardiogram returns to normal. These variations in the effects of coronary occlusion are clearly related to the size of the occluded vessel, the rate at which occlusion develops, and the capacity to provide a collateral circulation. Blumgart *et al.* (1950) found inter-arterial communications in 15 per cent of healthy hearts. Laubry and Soulié (1950) found these in 4 out of 5 healthy hearts from patients under 30, 16 out of 49 at ages between 40 and 70, and 4 out of 14 at ages over 70; in healthy hearts they were small but in hearts with coronary disease they were much larger.

If we assume that " coronary episodes " are associated with partial or complete occlusion of a larger or smaller coronary vessel, and that the subsequent development of infarction depends on inability to produce an adequate collateral circulation, we can explain the differences between males and females on the assumption that both sexes start life with a capacity to provide a collateral circulation which is sufficiently well developed to prevent infarction in approximately half the instances of coronary occlusion:

females apparently retain this capacity throughout life, but males seem to lose it to a large extent once the age of 50 has been passed.

Mortality. When the differences in ætiology and behaviour of coronary artery disease in the two sexes are considered it would indeed be surprising if the mortality rates were uniform. Table I gives the mortality during the first six weeks after a cardiac infarct for males and females at different age periods, in our " pre-anticoagulant " series. In males, the mortality is quite low below the age of 50 (under 5%); there is a steady rise thereafter until the age of 65 when the figure reaches 35 per cent. The total number of females in the series is too small to allow comparison between different age groups; but the figures, such as they are, suggest that in females the mortality is much more uniformly spread over the different age groups, and that the rise in mortality with increasing age is indeed small (Table I).

The rising mortality with increasing age in males, and the more level mortality at all ages in females, accords well with the suggestions already made regarding the capacity to produce a collateral circulation in the two sexes. On the other hand the total mortality in females at all ages from cardiac infarction is

TABLE I

MORTALITY IN THE FIRST SIX WEEKS AFTER CARDIAC INFARCTION. INFLUENCE OF AGE AND SEX
(1930–50 " Pre-anticoagulant " Series)

Sex and age		Cardiac infarction					
		Total seen	Cases traced	Died	Mortality		
Males	30–44	25	22	1	4·6%	Age 30 to 54 — 6·8%	Age 30 to 59 — 8·2%
	45–49	25	25	1	4·0%		
	50–54	45	41	4	9·8%		
	55–59	69	58	6	10·3%	55 to 64 — 13·6%	
	60–64	54	45	8	17·7%		
	65–69	29	23	8	34·7%	65 to 85 — 35·2%	60 to 85 — 25·6%
	70–85	19	18	6	33·3%		
	Total	266	232	34	14·8%		
Females	30–49	7	7	2	—		30 to 59 — 23·5%
	50–59	11	10	2	—		
	60–69	20	15	4	—		60 to 85 — 28·0%
	70–85	10	10	3	—		
	Total	48	42	11	26·5%		

Note—Only 4 cases in this series received anticoagulants. A male, aged 47, died 6th day; a male, aged 59, survived one year; a male, aged 62, survived just over two years; a male, aged 63, alive when last heard of two years later. Exclusion of these 4 cases from the series would *emphasize* the difference in male mortality between the younger and older age groups.

almost double that in males. This finding is entirely unexpected, not only in view of the conclusions already reached regarding the capacity to provide a collateral circulation in the two sexes, but also having regard to the fact that females generally have a better life expectation than males of the same age. The severity of individual attacks will not explain the greater mortality in females in this series. The ratio of " severe " to " mild " attacks in males (117 to 111) and in females (23 to 21) was almost identical. (In 6 males the available information is inadequate to determine whether the attack was " severe " or " mild "; in two females the severity is known but the age has not been recorded.) Attacks were classified as " severe " if accompanied either by signs of shock or by symptoms of heart failure whether left-sided or right-sided. These two factors are of extreme prognostic importance, irrespective of age and sex, as shown by Table II.

TABLE II
INFLUENCE OF SHOCK AND HEART FAILURE UPON MORTALITY IN CARDIAC INFARCTION

Cardiac infarction	Present			Absent		
	Cases	Died	Mortality	Cases	Died	Mortality
Shock	112	36	32·1%	166	8	4·8%
Failure	73	23	31·8%	205	21	10·3%

Cardiac Ischæmia. During the corresponding period (1930–50) 167 cases were seen and diagnosed as cardiac ischæmia according to the criteria already enumerated; of these, 150 were followed for at least 6 weeks, some for as long as 15 years. In 17 cases (16 males) symptoms of infarction developed within 6 weeks of the onset; one of them died on the first day of his infarction, a male, aged 62; the remaining 16 survived the attack. These cases are already included in the tables as cases of cardiac infarction. In 133 cases of cardiac ischæmia no infarct followed during the first six weeks and the mortality in these cases was quite low. Of 93 males, two died within six weeks, one in the 50–54 and one in the 55–59 age group; of 40 females, two died, one in the 55–59 and one in the 60–64 age group. Thus the immediate mortality was 2·2 per cent for males, 5 per cent for females, and 3 per cent for both sexes combined in the cases of simple ischæmia. If the cases that started as ischæmia and subsequently developed infarct are included, the mortality was 2 per cent in males and 4·9 per cent in females.

However, the incidence of infarction in cases that start as ischæmia may in fact be higher than the foregoing figures would suggest. During the same period 117 patients who already had cardiac infarction when first seen gave a history of prodromal symptoms; some of them would no doubt have shown signs of infarction even in the prodromal period, but a number would have been diagnosed as ischæmia in this stage. It is suggested therefore that the incidence of infarction within six weeks of the onset of ischæmia is not greater than one in three and not less than one in ten. These figures are of importance in assessing the prophylactic use of anticoagulants to prevent infarction in cases of ischæmia.

It is of passing interest to note that the mortality was a little lower in cases of cardiac infarction with a history of prodromal symptoms (13%) than in those with abrupt onset and no warning (17%). A history of previous cardiovascular disease—hypertension, cerebral vascular lesions, angina of effort, or previous coronary episodes—increased the mortality of cardiac infarction from 13 per cent to 17·5 per cent.

The Long-Term Prognosis after Coronary Episodes. The first four weeks cover the most dangerous period after cardiac infarction; 40 out of 45 deaths occurred within the first 28 days and the majority of these took place in the first fortnight. The long-term prognosis becomes a problem once a patient has successfully weathered the first four dangerous weeks. The observations that follow are based on the fate of 240 patients who were still alive four weeks after the onset of their attack. Table III gives for each age group (i) the original number of survivors; (ii) the position at the end of the 1st, 3rd, 5th and 10th years; (iii) the latest year at the end of which half or more than half the patients traced were still alive; and (iv) the longest survival period so far reached.

Although the number of females is small, it would appear that the age at onset is the most important factor in determining the probable expectation of life; this was longest in the youngest age groups and diminished steadily with advancing age. Since there were relatively more women in the older age groups, women as a whole compared unfavourably with men; but when the age at onset is taken into consideration, the younger women (under 50) tended to outlive the men. In males, the optimum age from the point of view of life expectancy was from 50 to 54; these patients survived on the average for 6 years whereas those of 45 to 49 averaged only 5 years, and those under 45 only 4 years. A possible explanation may lie in the change of temperament that is apt to occur about the age of 50. The restriction of activity necessary after recovery from a cardiac infarct tends to be more trying and irritating to the younger man and may perhaps be less strictly observed by him. After the age of 55 the expectation of life diminishes rapidly although individual patients may survive for long periods. The worst expectation was at age 60 to 64; half the patients in this group died before completing their third year. Those between 65 and 74 fared somewhat better, but three of the four original survivors who were aged 75 or over had died within three months. It may here be remarked that Smith (1942 and 1953) followed up 100 consecutive cases for 20 years but observed no relationship between age and survival period.

TABLE III

FOLLOW-UP OF PATIENTS SURVIVING CARDIAC INFARCTION AND CARDIAC ISCHÆMIA MORE THAN FOUR WEEKS

	Alive after 4 weeks	Number traced and number alive at end of year				Half still alive at end of year			Longest survival	
		1	3	5	10	Year	Traced	Alive	Years	No
Infarcts										
Males										
30–44	23	17–12	16– 9	9– 2	3– 0	4	14	7	7	2
45–49	23	18–17	18–15	14– 8	3– 0	5	14	8	9	1
50–54	36	26–23	22–13	19–11	11– 2	6	19	10	14	2
55–59	56	42–33	40–23	32–12	11– 1	4	37	18	14	1
60–64	37	27–24	19– 8	15– 4	8– 1	2	23	16	14 (died 15th)	1
65–69	16	15–11	14– 7	12– 4	3– 2	3	14	7	20	1
70–74	9	7– 5	6– 4	4– 1	2– 0	4	4	3	5	1
75–85	4	3– 1	3– 0	3– 0	0	under 3 months			1	1
Females										
30–44	1	0								
45–49	5	3– 2	3– 2	3– 2	2– 1	10	2	1	17	1*
50–54	4	4– 4	3– 2	2– 1	1– 0	5	2	1	5	1
55–59	5	4– 2	4– 2	3– 0	1– 0	4	4	2	4	2
60–64	7	3– 2	2– 0	2– 0	2– 0	2	2	1	2	1
65–69	7	5– 4	4– 1	3– 1	1– 0	2	5	4	6	1
70–74	6	5– 1	5– 1	4– 0	1– 0	under 1 year			3	1
75–85	1	1– 0	1– 0	0		under 1 year			—	
Ischæmia										
Males										
30–44	15	12–11	10– 9	9– 7	5– 2	9	6	3	12	1
45–49	16	11–11	9– 8	6– 6	2– 1	10	2	1	10	1
50–54	19	11–11	10–10	6– 4	2– 1	10	2	1	15	1
55–59	16	9– 6	6– 3	6– 3	3– 0	8	5	3	9	1
60–64	16	8– 7	6– 5	4– 3	0	5	4	3	5	3
65–69	4	4– 4	4– 3	4– 3	1– 0	7	3	2	7	2
70–74	4	4– 4	4– 4	3– 2	2– 0	5	3	2	5	2
75–85	1	1– 1	1– 1	1– 1	0	5	1	1	6	1
Females										
30–44	3	2– 1	1– 0	1– 0	1– 0	2	2	1	2	1
45–49	2	0								
50–54	3	2– 2	2– 2	2– 1	0	5	2	1	5	1
55–59	5	2– 1	2– 1	1– 1	0	7	1	1	7	1
60–64	14	10– 9	6– 3	5– 2	4– 0	4	6	3	8	1
65–69	6	3– 2	3– 2	2– 1	1– 0	6	2	1	6	1
70–74	1	0								
75–85	4	2– 2	2– 2	2– 1	2– 0	5	2	1	5	1

* This patient developed an aneurysm of the left ventricle within 6 months of her original attack in 1937. She is still alive. The walls of the aneurysm have been calcified for at least the last three years.

The expectation of life after an attack of cardiac ischæmia is approximately twice as long as that after cardiac infarction. This was found in both sexes and at all ages with the exception of one group (females, 30 to 44) in which the numbers are too few to justify any conclusion.

Apart from age and sex, the factors affecting length of survival are shock or failure at the time of the original attack, and the previous history. Of these failure is the most important; half of the survivors from attacks accompanied by failure died within two years. Half the patients who survived an attack with shock had died before the end of the third year; and half those who gave a history of previous cardiovascular disease likewise died within three years.

Mode of Death. Information regarding 81 deaths is available either from the patient's medical attendant or from personal observation; the causes of death are summarized in Table IV, which also gives the numbers dying at specified intervals after the attack. In 44 cases the date of death has been obtained from the patient's acquaintances or from newspaper notices and the mode of death is unknown.

TABLE IV

MODE OF DEATH AND PERIOD OF SURVIVAL IN 81 CASES OF CARDIAC INFARCTION

Mode of death	Number	Interval after original attack					
		4–13 weeks	3–12 months	1–2 years	2–3 years	3–5 years	Over 5 years
Subsequent attack	25	4	2	4	4	6	5
Cardiac failure	23	5	11	3	2	1	1*
Sudden death	16	1	4	2	5	2	2
Embolism†	5	3	1	1			
Cerebral thrombosis	4	0	0	1	0	1	2
Bronchial carcinoma	3	0	2	1			
Carcinoma elsewhere	2	0	0	0	0	0	2
Prostatic uræmia	1	1					
Virus pneumonia	1	1					
Intestinal obstruction	1	0	0	0	0	1	

* Failure in this case was precipitated by a prostatectomy 9 years after the original attack.

† Excluding emboli that occurred during the first four weeks (36) emboli that occurred during subsequent attacks (7) and emboli during or immediately before fatal failure (4). There were also 5 instances of embolism occurring after the fourth week which did not prove fatal.

Almost one-third of the deaths occurred in a second or subsequent attack, and these deaths are more or less evenly spread over the ensuing years being only a little more common in the first than in later years. Cardiac failure accounted for nearly another third, but most of the deaths from this cause occurred within the first year. One death in every five occurred quite suddenly while the patient was engaged in his usual daily routine; these deaths again were spread over the years, being perhaps a little more common in the first and third than in other years. In view of the widespread apprehension regarding sudden death after cardiac infarction or ischæmia it is interesting to note that 180 patients were traced to the end of the first year after a cardiac infarct and four of them had died suddenly during the year. The corresponding figures after attacks of cardiac ischæmia are 81 traced of whom one died suddenly.

The occurrence of three deaths from bronchial carcinoma soon after a coronary thrombosis seems worthy of comment. I have knowledge also of a fourth case, not included in the series as he was never examined by me but was a friend of the family; he suffered from angina of effort for about two years before his death from bronchial carcinoma. A fifth patient was seen in 1954 with angina of effort and cardiographic signs of infarction; he is now suffering from a bronchial carcinoma. Finally, a sixth patient was referred to the outpatient department some years ago with a typical history of coronary thrombosis seven weeks previously, cardiographic signs of transmural anterior infarction, hæmoptysis, physical signs in the left lower lobe, and an X-ray shadow that was at first thought to be an infarct; serial X-ray examinations over the next few weeks demonstrated that the lesion was a bronchial carcinoma. This incidence of bronchial carcinoma after cardiac infarction seems much too high to be purely accidental. It will be noted, moreover, that the deaths from bronchial carcinoma occurred within two years, whereas the two deaths from carcinoma elsewhere took place more than five years later. It seems likely that in these cases the original coronary thrombosis was an early symptom of the developing bronchial carcinoma, analogous to the superficial or deep venous thrombosis that sometimes heralds the onset of this disease.

SUMMARY

The age incidence of coronary attacks has been compared in men and women in a series of 865 cases. In men the incidence starts earlier, reaches a high peak at age 55 to 59, and thereafter falls steeply.

In women the rise in incidence is slow and steady from age 40 to age 70; there is no ultimate fall in incidence comparable to that seen in men. One-half the "coronary episodes" in women result in infarction; one-half the coronary episodes in men under 50 result in infarction, but after the age of 50 three-quarters produce infarcts. The ætiological and pathological implications of these differences are discussed.

The immediate mortality in 276 cases of cardiac infarction which were treated before anticoagulants were adopted has been analysed in relation to age and sex. In men the mortality rises steadily from 5 per cent at ages under 44 to 35 per cent at ages over 65; in women the mortality is approximately 25 per cent in all age groups, rising only slightly as age advances.

The long-term prognosis has been studied in 240 survivors from cardiac infarction and 129 survivors from attacks of cardiac ischæmia. The best expectation of life was found in men aged 50 to 54 who fared better than younger men; the worst expectation was at age 60 to 64. In women the expectation was best at ages below 50 and diminished progressively as the age at onset increased. The ultimate cause of death and the time at which they are most likely to occur are also discussed.

The mortality and survival figures are intended as a basis of comparison with figures to be published dealing with a later series in which anticoagulants have been used for selected cases.

It is a pleasure to acknowledge the help of numerous general practitioners who have provided information regarding the subsequent history of patients with coronary disease referred by them: without their aid, this follow-up would have been impossible. I would also express my appreciation of the help given by my secretary Miss A. Watson, and by Mrs. E. Yarr at the Victoria Infirmary.

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THE HEART SOUNDS AND THE ARTERIAL PULSE IN CONGENITAL AORTIC STENOSIS

BY

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Congenital valvular and subaortic stenosis are relatively rare lesions; Abbott (1936) found subaortic stenosis in 12, valvular stenosis in 11 and atresia in 12 in a series of 1000 autopsies of congenital heart disease, and Wood (1950) made this diagnosis in 2 per cent of his cases of congenital heart disease. Campbell and Kauntze (1953) believe that congenital aortic valvular stenosis is commoner than has previously been considered to be the case; they found it in 3 per cent of 460 cases of congenital heart disease. Of the first 1500 cases of congenital heart disease seen at the Hospital for Sick Children, we have made a diagnosis of aortic stenosis in about 6 per cent. Since the prognosis is bad in the most severe cases and since some of these may be amenable to operation, an exact diagnosis of this condition is important.

Whereas the nature of the systolic murmur and its phonocardiographic appearance are well recognized (Leatham, 1951), the nature of the heart sounds in aortic stenosis is not so clearly understood. There is considerable difference of opinion about the loudness of the second sound in the aortic area, and the nature of the first heart sound has not been clearly defined. This investigation is concerned with an analysis of the heart sounds in aortic stenosis by phonocardiography and a description of the typical arterial pulse.

MATERIAL

The investigation included fifteen patients with congenital aortic stenosis, 9 males and 6 females; twelve were children between the ages of 6 and 15 years and the remaining three were young adults. There was no doubt about the congenital nature of the lesion in every case, as the murmur had been first noted in infancy or early childhood. The diagnosis was made on the accepted clinical and radiographic criteria (Young, 1944; Grishman *et al.*, 1947; Wood, 1950; Brown, 1950; Campbell and Kauntze, 1953). All patients had a systolic thrill and harsh loud systolic murmur in the aortic area transmitted up ~~into~~ the right side of the neck; in one there was also an aortic diastolic murmur. Differentiation between valvular and subaortic stenosis was not found to be possible on clinical, radiographic or electrocardiographic grounds. The phonocardiograms of twenty-five normal children have also been studied to estimate the normal degree of splitting of the second heart sound in the pulmonary area.

METHODS

Phonocardiograms, with three different frequency responses, were recorded from each patient. Those designated high frequency in the illustrative tracings are approximately the same as the logarithmic phonocardiogram of Rappaport and Sprague (1942) in their frequency response. The medium- and low-frequency tracings represent rather lower frequencies than are ordinarily heard through a stethoscope. Recordings were taken from the apex, fourth and second left intercostal

spaces and second right intercostal space on a six-channel Elmqvist " Klinik " recorder. As reference tracings, lead II electrocardiograms and carotid artery tracings were recorded. The arterial tracings were obtained with a metal stylus resting on the suprasternal notch overlying the artery, impulses being transmitted directly to a crystal of Rochelle salt and the voltage so produced being amplified and subsequently recorded by a mirror galvanometer. There was no time lag in this circuit. This was estimated by bursting a balloon with a hot needle at a point equidistant from the metal stylus and a microphone; the deflection on the pressure tracing caused by the impact of the explosion was exactly synchronous with the initial vibration produced by the sound on a phonocardiogram. Allowance had to be made, however, for delay in pulse wave transmission from the aortic valve to the point where the recording was taken from the carotid artery. Assuming this to be an average distance of 10 cm. and allowing a pulse wave velocity in the ascending aorta of 3 metres/sec. (Bazett *et al.*, 1935), this delay would be about 0·03 sec. in a child. One of us (U.R.) has confirmed this finding of a delay of pulse wave transmission in the ascending aorta of about 0·03 sec. in normal subjects, by comparing electrokymograms taken at the same heart rate from the base of the ascending aorta and from the aortic arch. We have also made this comparison in three of the patients with congenital aortic stenosis (Fig. 1). The point of upstroke of the aortic arch tracing followed that of the tracing from the base of the ascending aorta by 0·03, 0·04, and 0·06 sec. respectively. We have thus allowed 0·03 sec. delay in all tracings when calculating the timing of the upstroke on the carotid arterial pulse that denotes the onset of systolic ejection into the aorta.

In four patients, timing of the components of the heart sounds against mechanical events in the cardiac cycle was made by recording synchronous border electrokymograms with the phonocardiograms. The electrokymograms were taken from the base of the ascending aorta and pulmonary artery and from the left and right auricular appendages. The electrical delay in this circuit compared with the phonocardiogram was 0·01 sec. This was estimated by feeding an electric signal to the inputs of the electrocardiogram, phonocardiogram, and electrokymogram amplifiers. The response of each was recorded simultaneously and showed no time lag between the electrocardiogram and the phonocardiogram, and 0·01 sec. lag of the electrokymogram behind these two tracings. Consequently, an allowance of 0·01 sec. has been made in all tracings for this delay.

Results

The First Heart Sound. Auscultation revealed what appeared to be accentuation of the first sound in all these patients, this accentuation being most easily heard at the apex. In several patients, the sound appeared to be widely split with the accentuation involving the second component of this splitting.

Phonocardiography revealed, in all but one patient, two distinct components at the apex following soon after the Q wave on the electrocardiogram (Fig. 2). These components were separated by an average of 0·05 sec. The *first component* followed the Q wave by an average of 0·05 sec., was best recorded at the apex

TABLE I

Relationship of Sounds Immediately following the Q wave to events in the Cardiac Cycle in Congenital Aortic Stenosis

Interval	Average duration (secs.)	Range	No. of patients
Separation of two components	0·05	0·04–0·09	14
Q—First component	0·05	0·02–0·07	14
Q—Estimated aortic valve opening (calculated from carotid and aortic electrokymogram tracings) ..	0·08	0·06–0·14	14
Q—Second component	0·10	0·06–0·16	15
Aortic valve opening—second component..	0·02	0·01–0·05 (Synchronous in 2 cases)	14

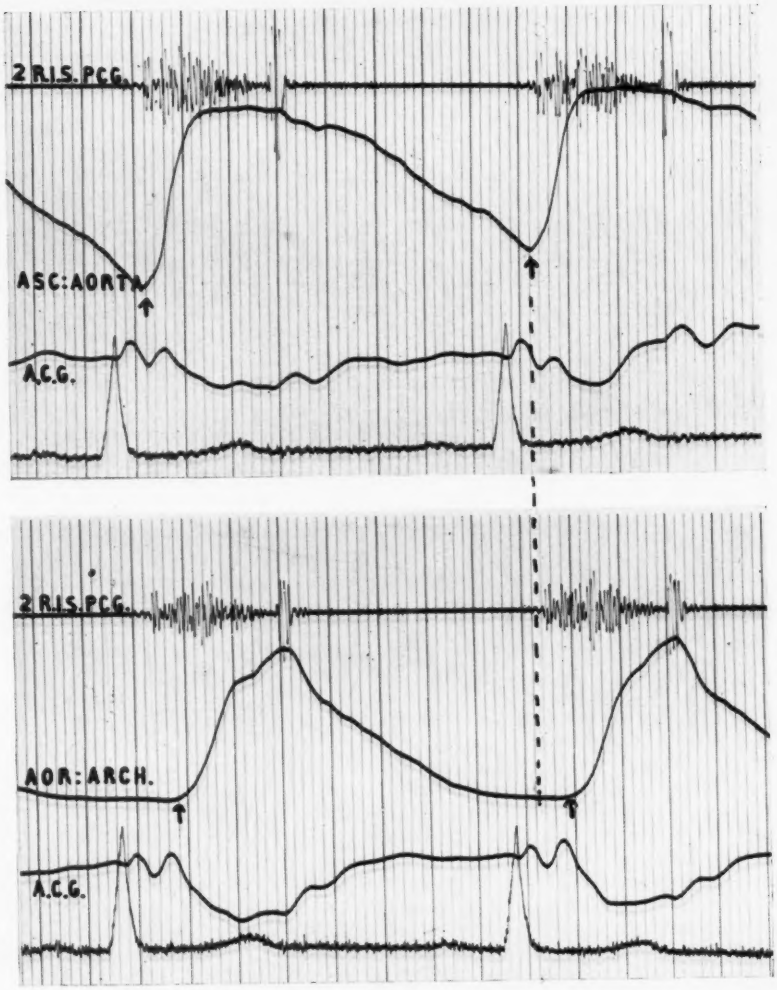

FIG. 1.—Border electrokymograms from the base of the ascending aorta and from the aortic arch, illustrating the delay due to pulse wave transmission in the ascending aorta in a case of congenital aortic stenosis. 2 R.I.S. PCG = Phonocardiogram from the second right intercostal space. A.C.G. = Apex cardiogram. Time intervals in this and all subsequent records are 0·1 and 0·02 sec.

in all instances and was of rather high amplitude in 6 patients. It preceded the calculated time of onset of systolic ejection into the aorta by an average of 0·03 sec.

The *second component* followed the Q wave by an average of 0·10 sec., and was of maximum amplitude at the apex in all cases. In the majority of patients it was also registered at the second right intercostal space, but with less amplitude (Fig. 3). It was of high amplitude in fourteen out of the fifteen cases, being consistently of much higher amplitude than the first component. It was invariably of rather high frequency (150–200 cycles per sec.) and in all instances, it occurred immediately before the onset of the systolic murmur.

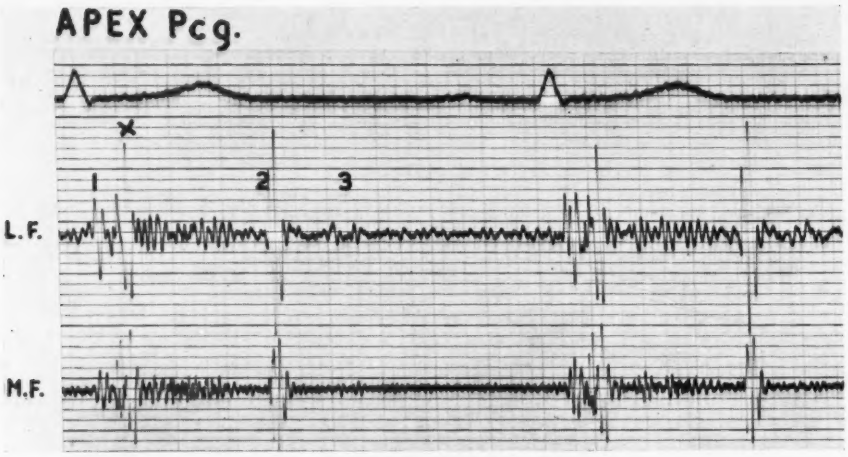

FIG. 2.—Apex phonocardiogram from a patient with congenital aortic stenosis, showing the separation of the two sounds immediately following the Q wave. X = Aortic systolic ejection sound. L.F. = Low frequency. M.F. = Medium frequency. 1 = First heart sound. 2 = Second heart sound. 3 = Third heart sound.

In 9 patients it was related to the time of opening of the aortic valves as calculated from the carotid tracing, and it was found to occur after the estimated time of aortic valve opening and the onset of systolic ejection into the aorta in all but one, the average delay being 0·02 sec. (Fig. 4). Therefore, it cannot be regarded as being part of the normal major components of the first heart sound as defined by Dock (1933) and Leatham (1954).

Timing of First Sound and early Systolic Components by Electrokymography. From its relationship to the Q wave on the electrocardiogram and to the upstroke of the carotid pulse, it seemed probable that the first component of the first sound was due to auriculo-ventricular valve closure. From the fact that it was best registered at the apex, mitral valve closure seemed to be the likely origin of this sound (Leatham, 1954). The relationship of the second component to the Q wave, its maximum intensity at the apex and its relation to the calculated time of onset of left ventricular systolic ejection made it seem probable that it was an early aortic systolic ejection sound.

Electrokymograms synchronous with the phonocardiograms were taken in four of these patients in an attempt to time these events more accurately. Luisada *et al.* (1948) have shown that the beginning of the upstroke following the nadir of the auricular systolic wave on the left auricular electrokymogram (Fig. 5) denotes the onset of isometric ventricular contraction and closure of the mitral valve. In two patients where the comparison was made, this point coincided with the onset of the first component on the phonocardiogram following the Q wave. It seems probable, therefore, that this sound is due to mitral valve closure.

In four patients, the point of onset of systolic ejection into the aorta was measured by an electrokymogram taken low down from the base of the ascending aorta (Fig. 5). As this tracing was calculated to have been taken from immediately above the aortic valves, no allowance had to be made for delay in pulse wave transmission. The initial vibrations of the second component were found to occur 0·02, 0·03, and 0·03 sec. after the onset of aortic systolic ejection in three patients; and the two events were synchronous in the fourth patient.

The Second Sound. By auscultation the second sound appeared to be normal or accentuated at the second right intercostal space or at the apex in all but one of these patients. At the second left intercostal space definite splitting of the second sound was only detectable in two patients. Phonocardiographic confirmation of these impressions was difficult as there was no calibration, but an attempt at estimating the

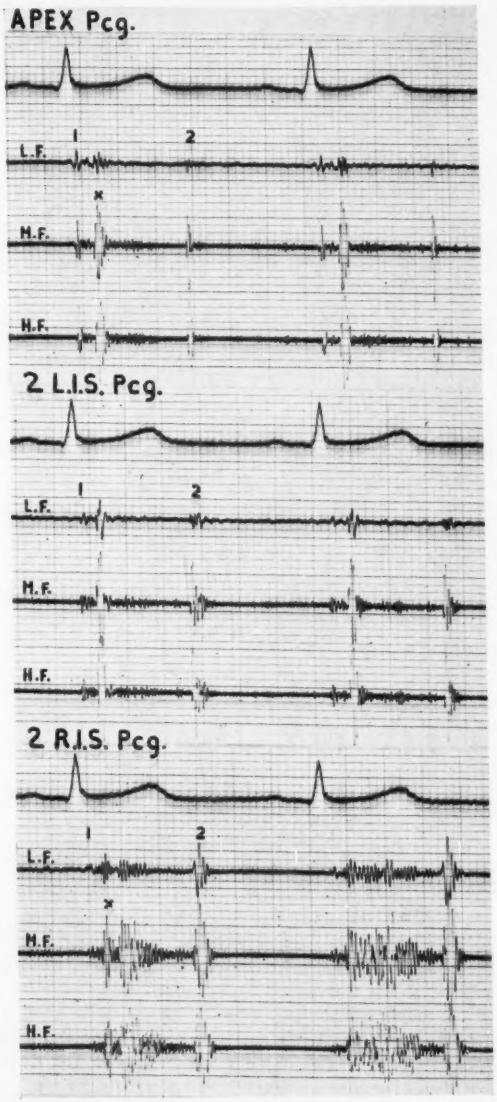

FIG. 3.—Phonocardiograms from the apex, second left intercostal space (2 L.I.S.), and second right intercostal space (2 R.I.S.) in a case of congenital aortic stenosis. The aortic systolic ejection sound (x) is well registered in all areas; it is uncommon for it to be so well recorded at the second left intercostal space. The rhomboid murmur at the second right intercostal space, ending before the second sound, is well shown in this recording. H.F. = High frequency.

amplitude of the aortic second sound was made by comparing the height of its components against that of the other sounds in the same complex. By this means, the aortic component of the second sound appeared to be normal in six patients and accentuated (Fig. 6) in eight patients. It was diminished in amplitude in one patient, who was not the one with associated aortic incompetence. It was best registered at the second right intercostal space in eight patients and at the apex in the remainder.

At the second left intercostal space, in fourteen patients, the aortic and pulmonary components were

separate in nine and fused in five instances. The average interval between the onset of the two components was 0·02 sec. The average interval between the onset of these two components in twenty-five normal children was 0·04 sec. All these figures refer to tracings taken in mid-respiration.

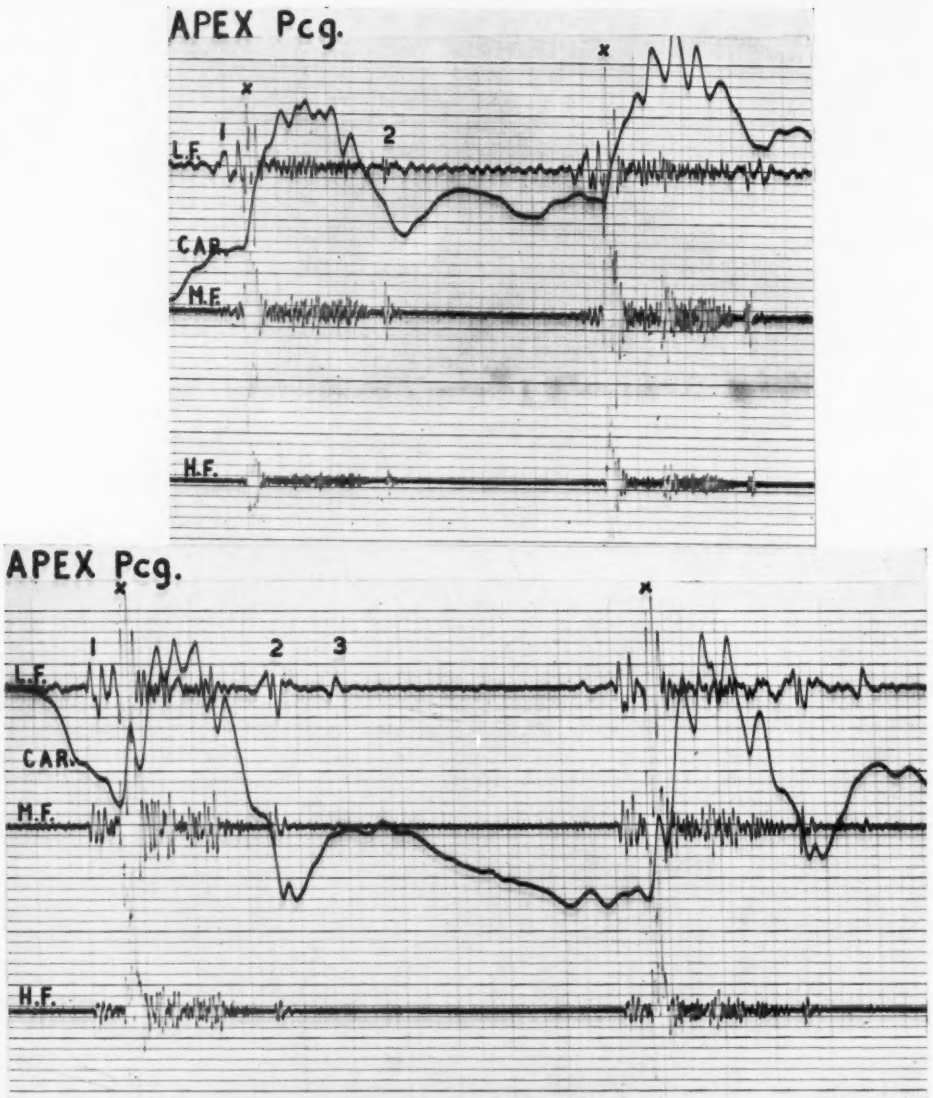

FIG 4.—Apex phonocardiograms from two patients with congenital aortic stenosis to show the relationship of the aortic systolic ejection sound (x) to the onset of systolic ejection into the aorta, calculated from the carotid (Car.) pulse. The delay due to pulse wave transmission from the aortic valves to the suprasternal notch is 0·03 sec.

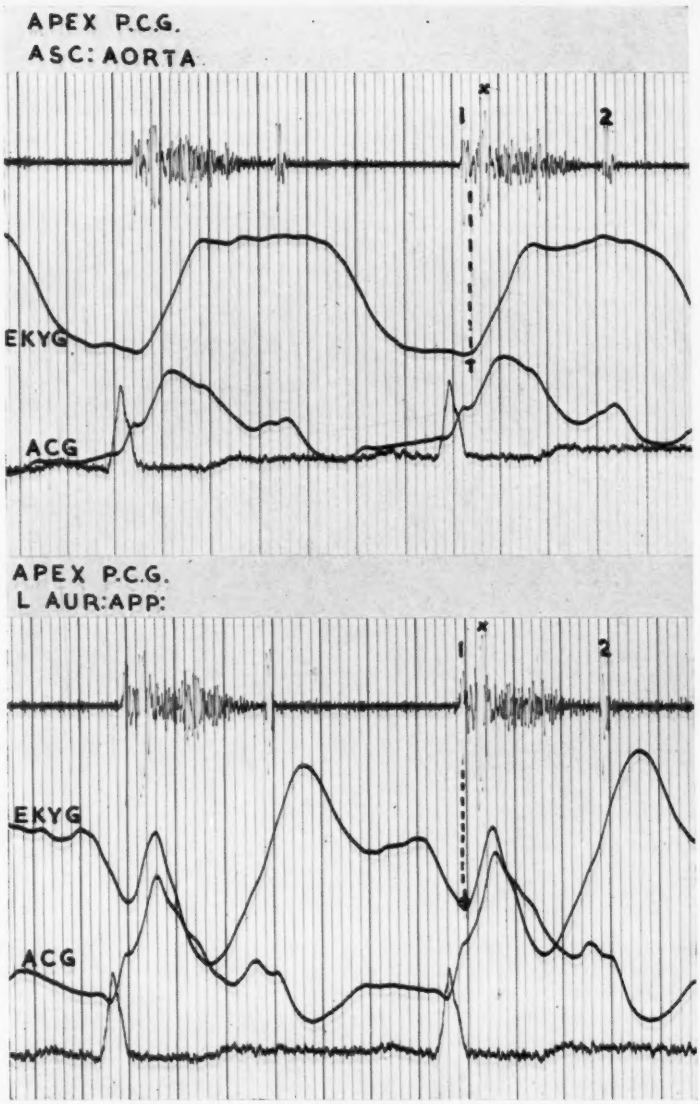

FIG. 5.—Synchronous apex phonocardiograms, apex cardiograms, electrocardiograms, and border electrokymograms from a patient with congenital aortic stenosis. The upper recording shows that the major vibrations of the first sound (1) precede the onset of systolic ejection into the aorta, indicated by the upstroke (↑) on the electrokymogram (Ekyg.) taken from the base of the ascending aorta. The second group of high-frequency vibrations (x) occurs 0·03 sec. after the onset of aortic systolic ejection.

In the lower recording, the onset of isometric ventricular contraction and closure of the mitral valve (↓) on the left auricular appendage electrokymogram (Ekyg.) is exactly synchronous with the first sound.

TABLE II
THE SECOND SOUND IN 15 CASES OF CONGENITAL AORTIC STENOSIS

Amplitude			Max. Registration		Splitting at 2 LIS.		Splitting at 2 LIS. in 25 normal children	
Normal	Accentuated	Diminished	Apex	2 RIS.	(sec.)	Range	(sec.)	Range
6	8	1	7	8	0·02	(0·02–0·03)	0·04	(0·03–0·05)

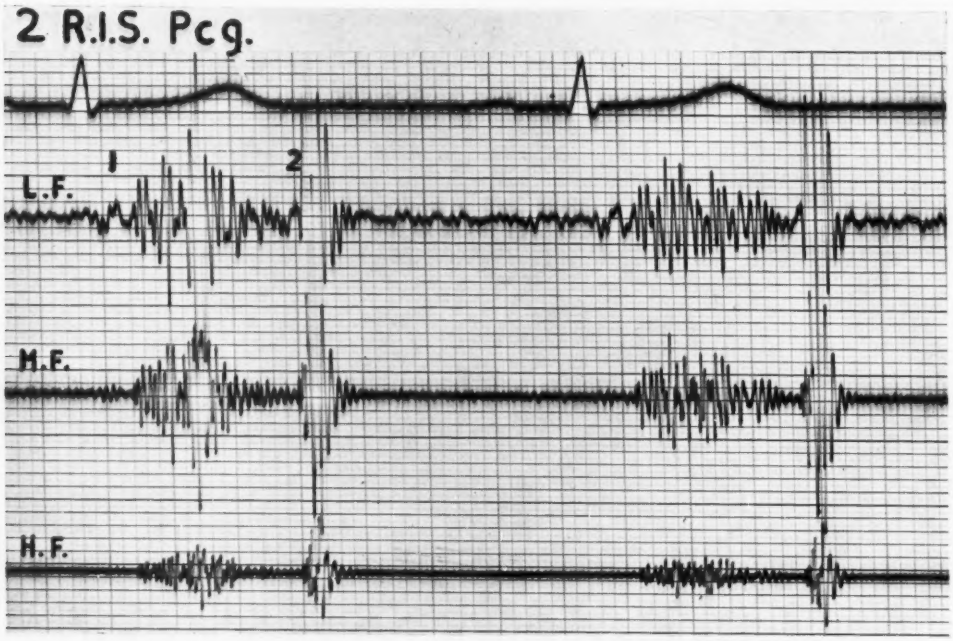

FIG. 6.—Phonocardiogram from the second right intercostal space in a case of congenital aortic stenosis, showing high amplitude of aortic second sound (2).

THE ARTERIAL PULSE

The carotid arterial pulse, recorded from the suprasternal notch, was studied in ten patients; in one there was aortic incompetence as well as stenosis. An anacrotic notch was present, one-third to half-way up the ascending limb of the pulse wave in eight instances (Fig. 7); in six it was well marked and in two it was present as a slight inflection of the upstroke of the pulse. The maximum height of systolic ejection was reached at about mid-systole in the majority of cases. The major portion of systole was occupied in the pulse tracing by low-frequency vibrations originating from the systolic murmur and giving a cock's comb appearance to the pulse wave. These vibrations have been called carotid shudder (Evans and Lewes, 1945), and they were present in all ten patients. The dicrotic notch was well marked in nine patients, and was absent in the one who also showed evidence of aortic incompetence.

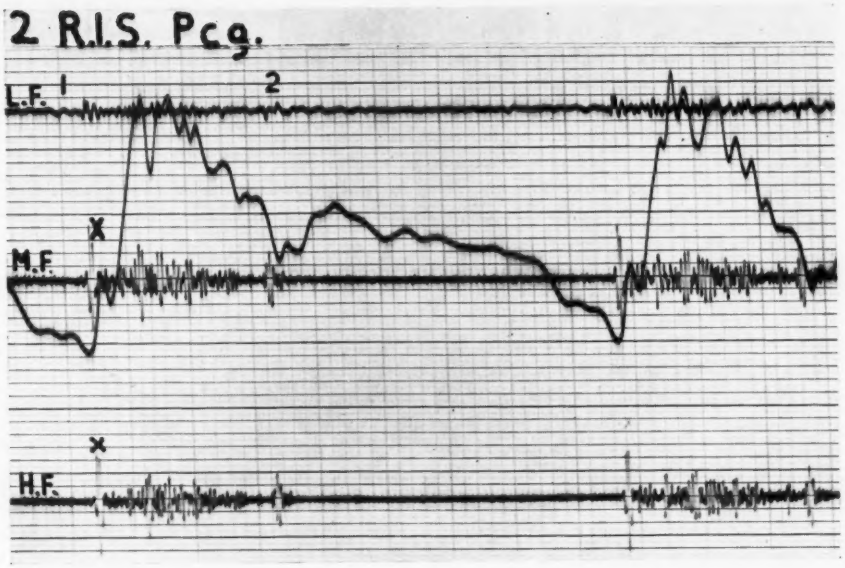

FIG. 7.—Phonocardiogram from the second right intercostal space in a case of congenital aortic stenosis showing the character of the carotid pulse. In this case the aortic second sound was of low amplitude.

DISCUSSION

On auscultation, we have been impressed by the common occurrence of what appears to be an accentuated first heart sound at the apex in cases of congenital aortic stenosis. Moreover, in some patients it is possible to detect wide splitting of the first sound, and in these the accentuation is of the second component. This can be distinguished from the narrow splitting of the first sound at the apex (0·02–0·03 sec.) heard in normal subjects (Leatham, 1954). Analysis of these sounds in aortic stenosis by phonocardiography has shown two distinct components in most cases, separated by an average of 0·05 sec. The first component appears to coincide with the moment of mitral valve closure and is of rather high amplitude in some cases. The second component does not appear to be part of the first heart sound, as it occurs after the onset of aortic systolic ejection. It is believed to be an aortic systolic ejection sound; and does not appear to be directly related to opening of the aortic valve as has been suggested previously (Wolferth and Margolies, 1945; Reinhold and Nadas, 1954). A similar sound has been described in cases of systemic hypertension, aortic stenosis and incompetence (Lian *et al.*, 1941; Leatham and Vogelpoel, 1954) and aortic aneurysm (Wolferth and Margolies, 1945). It seems to be analogous to the early systolic sound heard with dilatation of the pulmonary artery (Lian and Welti, 1937; Leatham and Vogelpoel, 1954), and is distinguishable from this by the fact that it is best heard at the apex.

It has been stated that the aortic second sound is normal in subaortic stenosis and diminished in valvular aortic stenosis (Brown, 1950; Wood, 1950; Brofman and Feil, 1952). Grishman *et al.* (1947), however, did not find that variations in intensity of the sound were of value in differentiating between these two types of stenosis and they were the first to emphasize that accentuation of the second sound was occasionally present in this disease. Lewes (1951) has also described one case of aortic valvular stenosis, proved at autopsy, with an accentuated aortic second sound. In our fifteen patients the aortic second sound was accentuated or normal in all but one instance. It is difficult to explain the accentuation of this sound in cases of subaortic stenosis with normal aortic

valves unless the dilatation of the aorta allows for better transmission of sound to the surface of the chest (Wolferth and Margolies, 1945). Splitting of the second sound in the pulmonary area was not detectable in the majority of these patients and the average time interval between aortic and pulmonary valve closure was 0·02 sec. This was half the average interval in twenty-five normal subjects and this difference may be due to delay in aortic valve closure in aortic stenosis owing to slight prolongation of left ventricular systole. This would then be analogous to the delay of pulmonary valve closure in pulmonary stenosis (Leatham, 1954).

The pattern of the carotid pulse taken from the suprasternal notch is characteristic in this condition (Grisham *et al.*, 1947; Brofman and Feil, 1952), owing to the rather marked anacrotic notch and the presence of carotid shudder.

We have not attempted to differentiate between valvular and subaortic stenosis in these children as we know of no way of doing so save at autopsy or possibly at operation. If it is true that a normal aortic second sound and a well marked dicrotic notch on the arterial pulse tracing indicate subaortic stenosis (Brofman and Feil, 1952), then fourteen out of our fifteen cases would fall into this group, but we believe that, at present, there is not sufficient evidence to enable us to make this differentiation.

Summary

A loud early aortic systolic ejection sound was heard and recorded at the apex in fifteen patients with congenital aortic stenosis. In six patients there was an impression of wide splitting of the first heart sound at the apex due to the aortic systolic sound following the mitral valve closure component of the first sound after an interval of 0·05 sec.

The second heart sound in the aortic area appeared to be normal or accentuated in all but one patient; and the interval separating the aortic and pulmonary components of the second sound in the pulmonary area was less than normal, giving the impression of a single second sound on auscultation in many instances.

The arterial pulse recorded from the suprasternal notch showed an anacrotic notch in the majority of patients and coarse vibrations synchronous with the systolic murmur in every case.

We would like to thank Dr. Aubrey Leatham for his helpful criticism of this work, and Mr. G. H. Bryant for his technical advice and assistance.

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THE PATHOLOGY OF ENDOMYOCARDIAL FIBROSIS IN UGANDA

BY

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Rare examples of heart failure due to extensive endocardial sclerosis have been reported from various countries in the last half century; in Uganda, however, this is one of the commonest causes of heart failure. The first indication that this condition was prevalent amongst Africans was given by Bedford and Konstam (1946), who had seen it in African troops. Independent pathological observations were made in Uganda and reported shortly afterwards (Davies, 1948, *a* and *b*).

In this paper a detailed description is given of the pathology of the disease, based on 32 necropsies. Over 100 have been performed on this condition since 1946 at Mulago, but unfortunately much of the collected material was destroyed in an explosion in the Medical School in 1951. Nineteen of the 32 necropsies analysed here were found in the 550 necropsies performed in 1953 (i.e. 3·5 %). Endomyocardial fibrosis was responsible for 33 of the 231 deaths from cardiac failure in the period 1951–53 (i.e. 14 %). Only hypertension, and that mainly renal, caused a higher proportion of heart failure. The third common cause of heart failure was syphilitic aortitis. Rheumatic heart disease is less common than in European series (though the pathological lesions do not differ), atheromatosis and essential hypertension are much less common, and coronary thrombosis in Mulago is very rare indeed (Williams *et al.*, 1954).

The 32 hearts on which the following description is based come from patients of both sexes and all ages (Table II). All were native Africans. The essential pathological lesion to be described in detail below is a *fibrosis of the endocardium of the ventricles*. On this, thrombus may be superimposed. The auriculo-ventricular valves are often involved by an extension of the lesion upwards from the apices of the ventricles (Table I).

TABLE I

MAIN ANATOMICAL AND CLINICAL SUBDIVISIONS OF ENDOMYOCARDIAL FIBROSIS

Region	Lesion	Clinical result
(1) L. ventricle	Endo- and myo-cardial fibrosis	Bilateral heart failure
(2) Mitral valve	Adherence of posterior cusp to ventricle	Mitral incompetence
(3) R. ventricle	Obliterative fibrosis	Pure right heart failure
(4) Tricuspid valve	Adherence of posterior cusp to ventricle	Tricuspid incompetence

The *pericardium* itself showed no abnormality. A small excess of pericardial fluid was common and a very large collection was found on one occasion (over 1500 ml.). In all these cases the fluid was clear and contained few cells, and only 2–4 g. of protein per 100 ml.

A depression over the apex of the right ventricle was visible in 16 hearts (Fig. 1); as this was associated with lesions of the endocardium in the right ventricle, it will be described in the section on that subject.

Heart Weight. The heart weight varied over an extraordinary range from atrophy to extreme hypertrophy. Adult male hearts ranged from 205 to 680 g. (mean 370 g.); adult female hearts from 185 to 260 g. (mean 212 g.); children's hearts were all greatly enlarged (Table II).

Muller's index (heart weight × 1000 ÷ body weight) was calculated and compared with normal indices for different ages and sexes in Europe (Rossle and Roulet, 1932). It was found that three hearts were atrophic (10–22 % below the normal mean). Of the rest one-third were normal in weight (±10%), one-third were moderately hypertrophied (10–30% above normal), and one-third were considerably hypertrophied (40–180% above the normal mean). These figures tend to be

TABLE II

A SUMMARY OF THE FINDINGS IN THE 32 NECROPSIES

No.	Sex	Age	B. W. (Kg.)	H.W. (g.)	Anasarca (graded 1, 2 or 3)	Duration of H.F. (months)	Chambers with E.F. (in order of severity)	Site of antemortem thrombus	Site of calcification	Valves involved
1	F	24	—	185	0	0	*RV*	0	RV	T
2	—	—	—	170	—	—	LV *RV*	LV RV	0	M T
3	—	—	—	370	—	—	LV RV	LV	0	M (pap.)
4	—	—	—	325	—	—	LV RV	0	LV (hist.)	M T
5	M	—	—	300	0	0	LV *RV* LA RA	LV LA RA	0	T (pap.) M (pap.)
6	M	35	54·4	240	3	4	LV RV	LV	0	M
7	M	35	47·6	524	2	3	LV *RV*	0	0	M T
8	M	40	52·3	445	1	½	LV RV	0	0	M T
9	M	30	59·9	640	2	9	LV LA	RV RA (hist.)	0	M
10	M	4	13·5	120	1	1	LV RV	LV	0	M
11	M	25	48·5	680	2	3	*RV* LV	RA LA LV	0	0
12	M	25	57·2	325	1	84	*RV* LV	RA	RV	T M
13	F	5	16·4	210	0	12	RV LA	0	0	M T
14	F	29	38·2	210	2	11	*RV* LV RA LA	0	0	M T
15	M	45	76·3	510	3	32	LV RV	RA LV RV	0	M
16	M	35	41·5	275	1	? 1	LV *RV*	0	0	M (steno sis) Aortic
17	M	30	38·3	230	0	0	LV *RV*	0	LV	0
18	M	60	60·0	355	2	1	LV *RV* RA	RA	0	M T
19	M	32	50·4	315	1	? 1	LV RV	LV	LV M	M T
20	M	30	42·9	320	3	5	LV *RV* RA	LV	0	M T
21	M	35	48·1	400	2	33	*RV* LV RA	RA	LV RV	T M (pap.)
22	M	60	54·0	320	0	0	LV *RV*	LV (hist.)	M	M T (pap.)
23	M	30	50·5	425	0	0	LV RV RA LA	RA	LV (hist.) LA (hist.)	T M (pap.)
24	M	55	33·0	205	3	9	*RV* LV	RV LV	LV (hist.)	T M
25	M	45	73·5	400	1	1	LV RV	0	LV	M T
26	M	47	55·0	270	2	44	*RV* LV RA	RA	0	T M
27	M	50	36·7	210	0	0	LV RV LA	0	M	M T
28	M	50	46·0	330	0	0	LV *RV*	LV	LV	M T (pap.)
29	F	35	44·0	260	3	1	*RV* LV RA	RV RA LV	RV (hist.)	M T
30	F	26	50·6	210	3	7	*RV* LV	RV M	0	T M (stenosis)
31	F	9	37·5	230	2	1	LV *RV* LA RA	LV (hist.)	LV	M T
32	M	30	65·6	435	3	3	LV *RV* LA	RA	M	M T

B.W.=Body weight. H.W.=Heart weight. H.F.=Heart failure. E.F.=Endocardial fibrosis. *RV*=Italic type shows that the RV lesion has produced obliteration. T=Tricuspid valve. M=Mitral valve. — =Unrecorded. pap.=papillary muscle only involved. hist.=lesion only visible histologically.

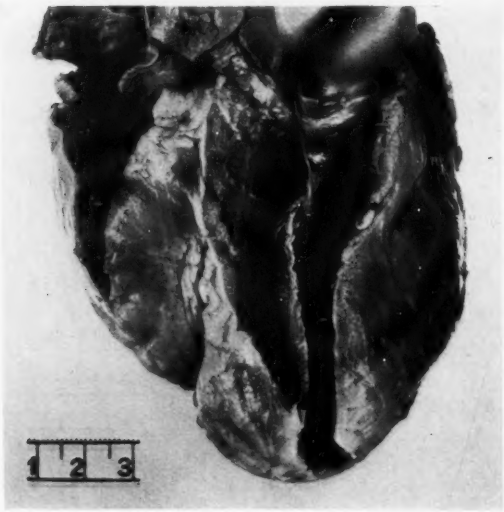

FIG. 1.—Deep depression over apex of right ventricle (Case 14).

lower than they should be as the presence of œdema adds false body weight and lowers Muller's index. Unfortunately we are ignorant of the normal heart weight for the different ages and sexes in the African.

No correlation with such factors as duration of heart failure or valve lesions has been found to suggest an explanation for these wide differences.

NAKED EYE APPEARANCES OF THE LESIONS OF THE LEFT SIDE OF THE HEART

The fibrotic endocardial lesions in the left ventricle will first be described; then the complications of thrombosis on the surface and calcification in the depths of the endocardium. It is logical to describe next the mitral valve as it seems that the lesions of this valve result from a spread of the ventricular lesions on to the chordæ and cusps, particularly the posterior. The result is usually incompetence, rarely stenosis. Finally, the minor left atrial lesions are described.

Left Ventricle. The endocardium of the left ventricle showed naked-eye lesions in 30 out of 32 hearts. In twelve all four walls and the apex showed fibrosis. The region most commonly involved was the posterior wall (29/30 cases), closely followed by the apex and lateral wall (both 25/30 cases); the septal wall was less frequently affected (15/30), and when it was the fibrosis was less in area and depth than on the other walls (Fig. 2 and 3). In the few cases where slight lesions were incidental findings in patients who had died of some other condition, they commonly took the form of a small patch of fibrosis at the extreme apex (Fig. 4). These were of pearly white fibrous tissue, often with a rugose surface, and with edges raised above the surrounding endocardium. More extensive lesions may also show this raised, rolled edge, beyond which there may be a filmy thickening of the endocardium. The maximal thickness of the endocardium was usually 2–3 mm., but it was occasionally as much as 10 mm. thick. Once or twice it showed a layered appearance in some areas, like agate. It was sometimes very firm at the raised edges and on the ventricular surface, but softer in the deeper layers where there was usually a thin layer of visible engorgement. Fibrous strands extended from the endocardial fibrous tissue into the myocardium in about

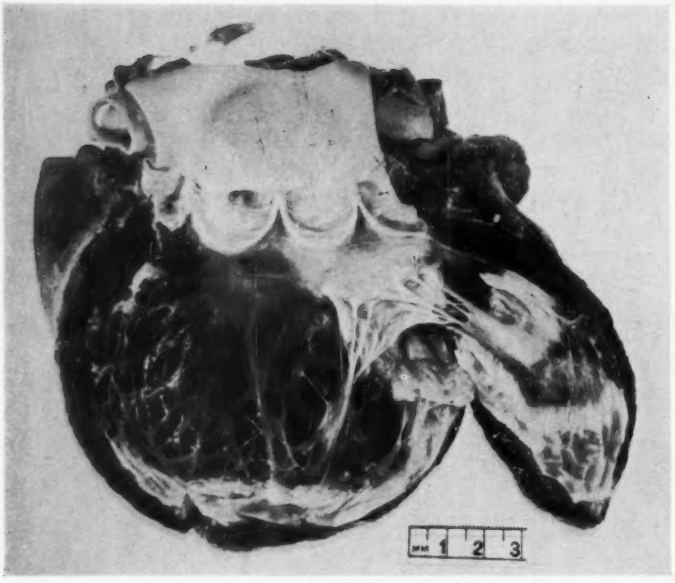

FIG. 2.—Left ventricle: smooth white fibrous tissue extending from apex up the posterior wall to the posterior mitral cusp, and also on to antero-lateral wall. The septum is characteristically spared (Case 26).

FIG. 2

FIG. 3.—Left ventricle: rugose fibrotic endocardium covers the apex, posterior, lateral, and anterior walls. Posterior mitral cusp completely adherent. Chordæ of anterior cusp thickened.

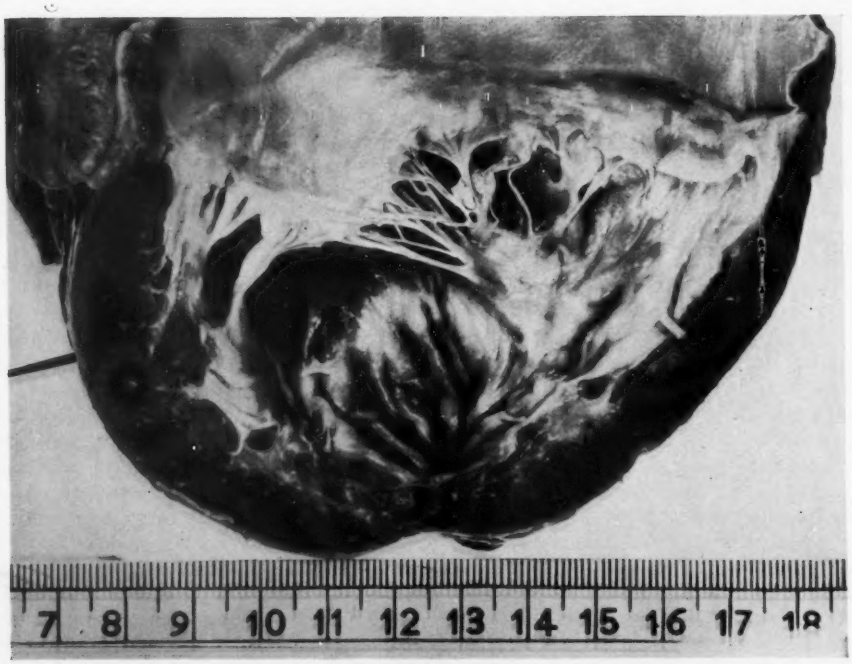

FIG. 3

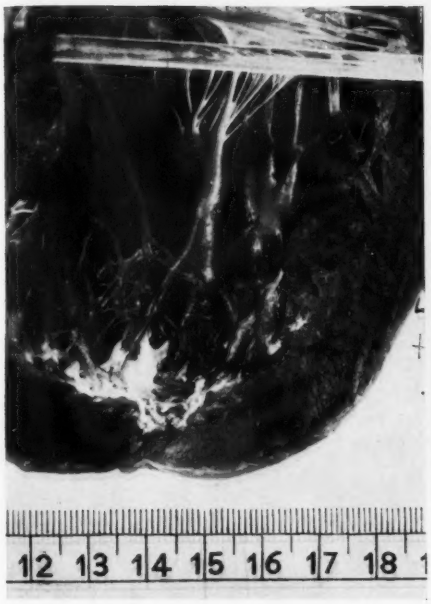

FIG. 4.—Left ventricle: small patch of fibrotic endocardium at extreme apex, found in a patient who died from uræmia (Case 23).

FIG. 5.—Left ventricle: note the flecks of fibrous tissue in the myocardium, and the way the papillary muscle has been surrounded and largely replaced by white fibrous tissue (Case 25).

one-third of the cases (Fig. 5). These were usually confined to the inner third but occasionally penetrated more deeply. The 30 left ventricular lesions were arbitrarily classified as follows.

(1) Mild in 7 (less than one-quarter of the endocardial surface being involved).

(2) Moderate in 11 (one-quarter to one-half being fibrotic).

(3) Severe in 12 (with fibrosis of more than half of the endocardial surface (Table III).

In 13 hearts the smooth white surface of the endocardial fibrosis was covered in part by mural thrombus in various stages of organization (Table IV). In nine the thrombus was only a thin layer varying from reddish-brown to yellow-green. In four there were masses of clot varying from 4 to 20 mm. in depth. The largest of these almost filled the ventricle, greatly reducing the cavity; such cases had been noted in a previous series (Davies, 1948, *b*). Mural thrombosis was much commoner when the endocardial fibrosis was extensive.

In nine left ventricles there were areas of calcification in the endocardial fibrous tissue, mostly as small granules, but in one case as a calcified plaque 2–3 mm. thick and 20 × 30 mm. in area (Fig. 6 and 7). Bacterial endocarditis was superimposed on the apical fibrosis in one heart.

In about one-third of the hearts the maximal thickness of the left ventricle lay between 15 and 18 mm.; this is slight hypertrophy on the criteria of Pagnoni and Goodwin (1952). This does not include three large hearts weighing 524, 640, and 680 g., whose maximal thicknesses were 8, 12, and 13 mm. respectively.

Mitral Valve Apparatus. The papillary muscle endocardium was more commonly involved than that over the chordæ or cusps (Table V). In 10 this was only slightly thickened, but in 9 one

TABLE III

INCIDENCE OF ENDOCARDIAL FIBROSIS IN THE DIFFERENT REGIONS OF 32 HEARTS

Region	Number	Percentage	Sub-divisions
Left ventricle	30	94	Mild 7 Moderate 11 Severe 12
Right ventricle	31	97	Mild 16 Moderate 6 Severe 9
Mitral valve *	25	78	Incompetence (i.e. posterior cusp adherent) 16 Stenosis as well 2 Minor lesions 9
Tricuspid valve *	23	72	—
Left atrium	7	22	—
Right atrium	9	28	—

* Excluding valves in which the papillary muscles only were affected.

TABLE IV

INCIDENCE OF VISIBLE MURAL THROMBUS IN THE FOUR CHAMBERS OF 32 HEARTS

Chamber	Number	Percentage	Sub-divisions
Left ventricle	13	41	Thin layer 9 Thick clot 4
Right ventricle	5	16	Thin layer 2 Thick clot 3
Left	2	6	—
Right	11	34	

TABLE V

INCIDENCE OF FIBROTIC LESIONS IN VENTRICLES AND A-V VALVES ARRANGED TO SHOW THE DIMINISHING INCIDENCE FROM VENTRICLE TO VALVE CUSP

Mitral valve	Cusp	Posterior 21	Anterior 15	
	Chordæ	,, 23	,, 12	
	Papillary muscles	28		
Left ventricle		30		
Tricuspid valve ..	Cusp	Posterior 14	Anterior 2	Septal 2
	Chordæ	,, 20	,, 8	,, 7
	Papillary muscles	,, 18	,, 16	— —
Right ventricle ..		31		

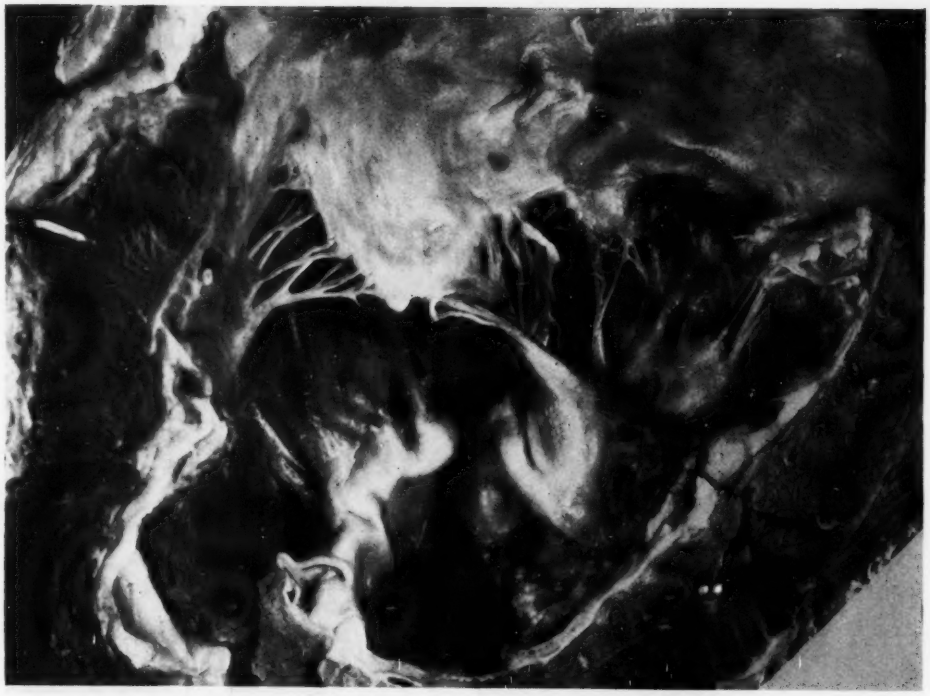

FIG. 6

FIG. 6.—Left ventricle: extensive, thick and calcified endocardial fibrosis; posterior mitral cusp adherent (Case 19).

FIG. 7.—X-Ray of isolated heart to show plate of calcium at the apex of the left ventricle (Case 19).

or both papillary muscles were more or less completely buried in white fibrous tissue. In 4 the muscular tissue of the papillary muscle was almost entirely replaced by fibrous tissue (Fig. 5).

When the chordæ are involved in the process, they become thickened and apparently shortened, with adhesion to each other and to the ventricular wall (Fig. 8). In the advanced lesion the chordæ of the posterior cusp may become completely embedded in a mass of fibrous tissue and both become functionless (Fig. 3, 6, and 9). The anterior group of chordæ, like the anterior cusp is less frequently affected, and although they fuse together they cannot for anatomical reasons adhere to the ventricular wall. In four instances chordæ had ruptured, and in three vegetations of bacterial endocarditis were found.

FIG. 8.—Mitral valve: posterior chordæ are fused to each other in a band and to the area of fibrotic endocardium beneath (Case 14).

FIG. 9.—Mitral valve: complete adhesion of posterior cusp and chordæ to thick underlying fibrous plaque. Margin of anterior cusp and some of anterior chordæ are thickened. The lesion in the lower part of the ventricle is unusually slight (Case 8).

Abnormalities of the cusps were usually associated with abnormalities of the chordæ. The posterior mitral cusp was abnormal in 21 hearts (Table V); in 12 of these it was completely immobilized by adherence to the posterior wall of the ventricle. Sometimes the end-result was a fibrous surface running straight down from the atrium to the ventricle and broken by no more than a slight irregularity where the cusp had become embedded (Fig. 3 and 9). In others the remains of the cusp projected as a short thick shelf. In four cases there was only partial adhesion of the cusp, and in five the cusp showed slight thickening without being adherent. The anterior cusp was less frequently and less severely affected, the usual lesion being a band of fibrous thickening along the free margin. Vegetations were present on four of these cusps, and microscopy demonstrated the presence of a superimposed bacterial endocarditis.

Four mitral valves showed slight calcification.

Mitral Incompetence. Incompetence was thought to have been present in 12 of the patients during life, as the entire cusp (in seven) or the greater part of it (in five) was found to be adherent; a further four with slighter adherence may have had some incompetence. The importance of the short posterior cusp in closing the mitral ring has been stressed by Brock (1952), and support is given to this view by the close correlation that we found in a previous study between clinical signs of incompetence and posterior cusp adherence (Ball *et al.*, 1954).

Mitral Stenosis. Two of the valves were stenosed, having maximal circumferences of 4 and 5 cm. respectively. In one of these a scarred and thickened aortic valve gave rise to a suspicion of rheumatic heart disease, as the aortic valve is almost always normal in endomyocardial fibrosis. Both these hearts showed characteristic endocardial fibrosis with typical histological lesions and no other evidence of rheumatism.

Left Atrium. Small patches of thickened endocardium with well defined edges were seen in the left atrium in seven hearts, three being in the appendage and three close to the posterior mitral cusp. The former are thought to represent completely organized thrombi. The latter three resembled MacCallum's patches; these three had all been diagnosed in life as having mitral incompetence, and this was confirmed in each by the nature of the valve lesions discovered. We concur with Brigden and Leathem (1953) in thinking that this lesion is due to the regurgitant stream of blood. Mural thrombosis was rare in this chamber, being found in only two hearts; in both the site was the appendage.

The maximal thickness of the wall in eight atria was 4 mm. or more; these were regarded as undoubtedly hypertrophied. A further ten were 3 mm. thick, a borderline measurement. There was a tendency for the hypertrophied atria to be associated with mitral incompetence, but there were many exceptions. Dilatation of the atrium was obvious in seven hearts.

Lesions of the Right Side of the Heart

The lesions in the right heart were in general similar to those in the left. The main difference was the development of obliteration of the cavity of the right ventricle when the endocardial lesion became extensive.

Right Ventricle. Endocardial fibrosis was present in the right ventricle in 31 out of 32 hearts; these could be divided into three groups of ascending severity.

(1) Mild in 16 cases (in which less than one-quarter of the endocardium was covered by visible fibrosis).
(2) Moderate in 6 cases (in which one-quarter to one-half of the surface was covered).
(3) Severe in 9 cases (in which more than half of the surface was covered).

The smallest lesions were invariably found between contiguous surfaces; in the crevices between adjoining trabeculæ carneæ or where a papillary muscle, chorda, or cusp touched the ventricular wall (Fig. 10). The sharply-defined plaques of fibrosis that characterize the early left ventricular lesion were rarely seen.

A striking feature of most of the moderate and all the severe lesions was the obliteration of the cavity produced by the advancing fibrosis. This is presumably at least partly due to the different anatomical configuration of the right ventricular apex, where most of the lesions started. In the most advanced cases the process had gone on to virtual obliteration of the inflow tract. The position of the apex thus moved progressively nearer to the tricuspid valve (Fig. 11, 12, 13, and 14). The lesion is best demonstrated by a series of coronal sections made at right angles to the plane of the septum. These usually reveal obvious penetrating strands of white fibrous tissue which indicate the position of the obliterated cavity. Sometimes a small, blind crypt, lined with endocardium, is left behind at the site of the original apex. When occasionally the fibrous strands are inconspicuous, the apposition of the septum and lateral wall produces a massive wedge of muscle (Fig. 16). Such an appearance was seen by Fienberg and Holzman (1951) in a heart that also had extensive endocardial fibrosis.

FIG. 10.—Tricuspid valve, medial end of posterior cusp and septal cusp. One of the chordæ has become completely adherent to a small patch of white fibrous tissue at a point where it crosses one of the trabeculæ carneæ (Case 23).

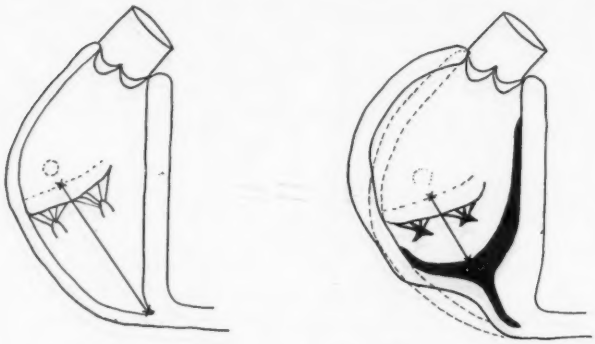

FIG. 11.—Diagram to show the main features of the obliterative fibrosis of the right ventricle. The relative length of the inflow tract is reduced from about 5–7 cm. in normals to about 2–6 cm.

One effect of this obliterative process was the drawing in of the anterolateral wall of the ventricle to produce the external depression previously mentioned (Fig. 1). This may be a deep crease, a saucer, or a triangular depression. It was always present when the right ventricular lesion was a severe one. It appeared that this indrawing of the myocardium was due to the approximation of the walls of the inflow tract with partial obliteration of the cavity. No external depression was seen at the apex of the left ventricle, even when there was extensive fibrosis of this chamber.

A means of measuring this obliterative process was devised; the distance was measured from the mid-point of the posterior tricuspid cusp at its attachment (a point just below the coronary sinus orifice), to the " apex," the point on the endocardium nearest to the lower end of the septum.

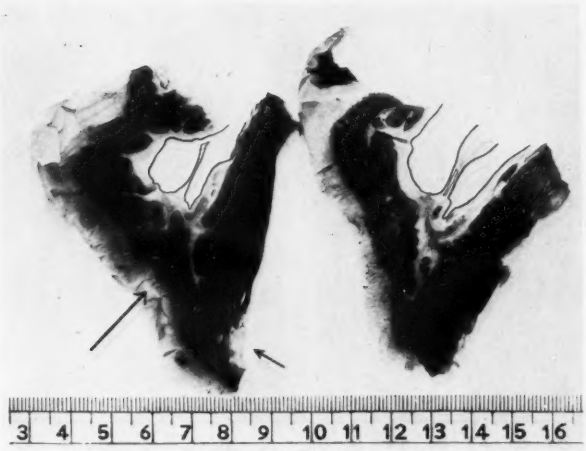

FIG. 12.—Sections through the apex of the right ventricle and septum. Fibrous tissue has filled up the apex and embedded the papillary muscle. The left-hand arrow indicates the characteristic external depression (covered by thick layer of epicardial fat) and the right-hand arrow points to a plaque of fibrous tissue at the apex of the left ventricle (Case 12).

In 16 normal hearts, the length of the inflow tract, thus defined, varied from 5·0 to 7·6 cm. In 17 hearts with obliteration of the right ventricle, the distance varied from 2·2 to 6·1 cm. These findings are shown in relation to the heart weights in Fig. 15.

Obliterative fibrosis was not always apical; in three hearts such a lesion was found on the septum, level with the tricuspid valve, producing an hour-glass constriction of the ventricle (Fig. 17). One of these lesions had caused an external depression.

Mural thrombosis, present in five instances, was relatively uncommon in this chamber. In two of these the thrombosis was massive, almost filling the inflow tract with greenish-yellow, fibrin thrombus, lightly attached to the endocardium. Calcification was also less frequent than in the left ventricle, occurring in four patients; one of these showed the most extensive calcified lesion found in this series, the calcium being deposited as numerous, bulky, granular masses, up to 15 mm. thick (Fig. 16 and 18).

Hypertrophy and dilatation were very common. As the apex was distorted, measurements were made at the infundibulum, and this showed mild hypertrophy in 18 hearts (5–7 mm.), moderate in 7 (8–10 mm.), and severe in 4 (over 10 mm.) (Pagnoni and Goodwin, 1952). It seemed possible that right ventricular hypertrophy might be related to mitral or tricuspid incompetence, but there was no correlation with adherence of the cusps of either valve. The isolated dilatation and hypertrophy of the right ventricle seen in cardiac beri-beri was not found.

Tricuspid Valvular Apparatus. Minor lesions of the papillary muscles, chordæ, or cusps were found in 26 hearts. The papillary muscles were involved in 19. The muscle may simply be surrounded at its base, or covered by a thin layer of fibrosis; or it may be engulfed in a mass of fibrous tissue, a mere nodule projecting to give rise to the chordæ (Fig. 12). The milder lesion is commoner in the anterior muscle, the severer in the posterior.

The tricuspid chordæ were abnormal in 20 valves, the common lesions being shortening, thickening, and adhesion to each other or to underlying patches of endocardial fibrosis (Fig. 10 and 19).

FIG. 13.—Right ventricle and tricuspid valve. The lesion is confined to the lower part of the inflow tract, which has become completely filled up with white fibrous tissue (Case 28).

FIG. 14.—Right ventricle: apex seen from above. The apex is obliterated and the large anterior muscle surrounded and covered with fibrous tissue. A dark layer of ante-mortem thrombus can be seen.

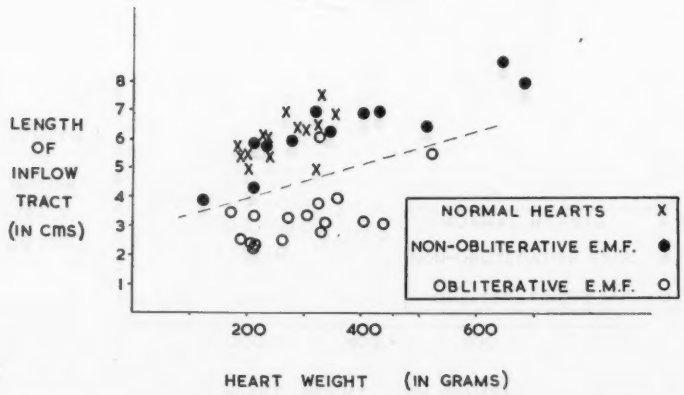

FIG. 15.—Right ventricle: length of inflow tract (as defined in the text), plotted against heart weight, in hearts showing obliterative fibrosis. The comparison with normal hearts shows that the obliterative fibrosis can halve the length of the inflow tract.

FIG. 16.—Section through the apex of the right ventricle, showing extreme obliteration of the inflow tract, deposits of calcium below the endocardium, which is only moderately thickened, and the massive wedge of muscle which has resulted from apposition of the walls of the right ventricle. The section has just gone into the left ventricle, the cavity of which is seen on the right of the picture. Thick layer of epicardial fat (Case 1). See Fig. 18 for X-ray of this heart.

FIG. 17.—Right ventricle, showing three patches of thickened endocardium. The largest, to which the arrow is pointing, is causing obliteration at the waist of the ventricle, between the inflow and outflow tracts (Case 11).

FIG. 18.—Radiograph of isolated heart, showing extensive granular deposits of calcium beneath the endocardium of the right ventricle, which has undergone advanced obliteration (Case 1).

Combinations of these lesions were common. The posterior chordæ were more frequently and more severely involved than the anterior and septal groups.

A common lesion in the cusps, which showed some abnormality in 14 cases, was adhesion of the posterior cusp to the ventricular wall; in the present series this was never so completely immobilized as the posterior mitral cusp. Since closing the series, however, we have seen two tricuspid valves in which the posterior cusp had completely disappeared beneath a sheet of white fibrous tissue; in both of these tricuspid stenosis was present, along with extreme obliterative fibrosis of the right ventricle and characteristic lesions of the left. In a smaller number the cusp was moderately thickened towards the free margin. Such thickening was less common in the anterior cusp and least of all in the septal.

Neither calcification nor bacterial endocarditis was found as a complication of the tricuspid lesions. Tricuspid incompetence can occasionally be diagnosed in life (Ball *et al.*, 1954).

Right Atrium. The endocardium showed focal areas of thickening with clear-cut edges in nine atria. Seven of these were close to organizing thrombus, and it is believed that they were the result of complete organization of small thrombi. In seven further cases there were ill-defined patches of slightly thickened endocardium of doubtful significance.

Ante-mortem thrombus was attached to the right atrial wall in 11 of the hearts. In some it was dark red and lightly attached, in others it was mottled yellow-red on section and partly organized, and in two it was covered with a layer of white fibrous tissue, the result of complete organization. The commonest site was the appendage.

FIG. 19.—Tricuspid valve and right ventricle. The posterior cusp of the valve is thickened and in places adherent to the underlying fibrotic endocardium. The chordæ are short, thick and fused. The lower part of the right ventricle is filled up with dark friable ante-mortem clot (Case 24).

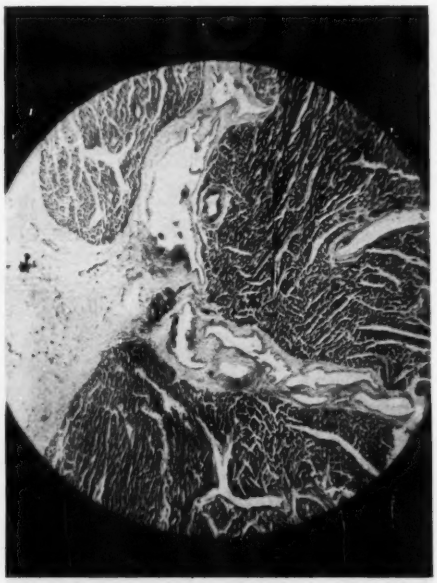

FIG. 20.—Dilated thin-walled blood vessels in the myocardium under a patch of endocardial fibrosis. The deeper part of the fibrous endocardium is seen on the left.

Hypertrophy and dilatation were both present in some two-thirds of the series. Two of the three atria that showed these changes most severely were associated with marked obliterative fibrosis of the right ventricle.

Semilunar Valves and Great Vessels. The pulmonary valve escaped completely and so did the aortic, except for the one case mentioned above. The great veins entering the atria showed no lesions.

The pulmonary arteries were normal save for occasional slight atheroma, and the same is true of the aorta. While we have not always made full measurements of the aortic calibre, our observations have not led us to associate this disease with aortic hypoplasia; this is common in East African natives (Dick, 1947). The major coronaries were normal; obliterative changes in the small branches are described below. No vascular defects have been noted in other regions of the body.

Histopathology of Ventricular Changes

The histological changes are extremely uniform despite variations in the gross appearance.

Mural Thrombus. This, consisting of fibrin alone or of all the components of a blood clot, was superimposed on the fibrotic endocardium in 21 of the 61 abnormal ventricles; in 18 of these it was visible to the naked eye (Table IV). It was often covered at its edges by endothelial cells and there was evidence of organization at the edges. Sometimes a ball of old thrombus completely encapsulated by fibrous tissue has been seen.

Endocardium. The greatly thickened mass of endocardial fibrosis showed three zones (Fig. 21). The superficial zone beneath the thrombus was usually acellular and often hyalinized. Deposits

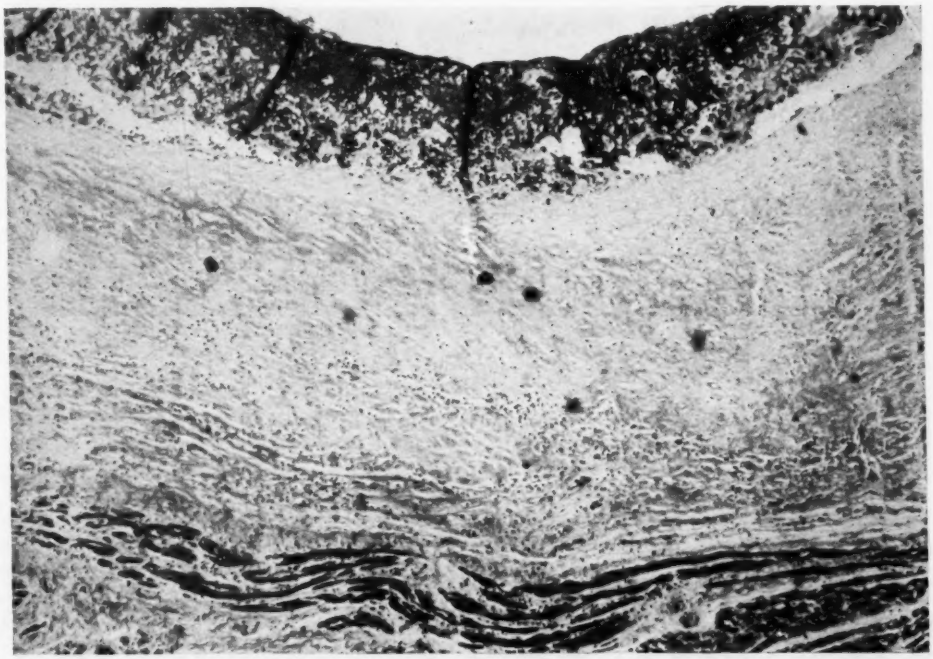

Fig. 21.—Section showing greatly thickened ventricular endocardium. Note the thin layer of mural thrombus, the layer of acellular fibrous tissue and the deeper zone of moderately cellular fibrous tissue. Fibrous tissue is invading the myocardium. Magnification, ×37. Case 6.

of calcium when present were in this layer. Deep to this was an intermediate zone of loosely-textured fibrous tissue containing an occasional macrophage, lymphocyte, or plasma cell, but rarely polymorphonuclear leucocytes or eosinophils. Next to the myocardium there was invariably a zone of small blood vessels, often with a few chronic inflammatory cells; we have called this the granulation tissue layer (Fig. 22). In this layer and in the layer above it, surviving degenerate muscle fibres were seen on occasion, usually in bundles but sometimes in isolation. Areas of irregular elastosis were rarely seen and when present were scanty and irregular in contrast to the picture in congenital fibro-elastosis.

FIG. 22.—Granulation tissue layer, between the fibrous endocardium and the myocardium; many small blood vessels are present and some chronic inflammatory infiltration.

Myocardium. The inner third of the myocardium showed the greatest abnormality both in its interstitial cells and parenchyma. Bands of fibrous tissue extending inwards from the fibrosed endocardium penetrated this region of the myocardium, cutting off bundles of myocardial fibres which showed degenerative changes. All hearts showed more or less fibrosis in the myocardium, and it is for this reason that we use the term endomyocardial fibrosis. In these fibrous bands many small blood vessels were seen but also numerous thin-walled, dilated vascular channels. We take these to be thebesian veins and arterio-luminal vessels (Wearn, 1941) which had become dilated from obstruction by endocardial fibrosis (Fig. 20). The myocardial fibrosis seems to develop around these vessels. The myocardial fibres themselves showed a combination of the following changes, atrophy with wavy loss of sarcoplasm, hyalin changes, interfibrillary œdema (" moth-eaten " fibres), and interstitial œdema. The nuclei were commonly enlarged and hyperchromatic and were often sharply rectangular or cigar-shaped; such nuclear changes were present in 27 of the 32 hearts. Special stains did not show fat or excess of glycogen. These muscle fibre abnormalities were found

in all chambers irrespective of the presence or degree of endocardial fibrosis, but were always most marked in the subendocardial region. Despite these degenerative changes acute necrosis of fibres and evidence of their removal was not seen.

A mild infiltration of the myocardium with lymphocytes and macrophages was common; it was abundant in 5, but absent in 18 ventricles. Polymorphonuclear infiltration was very unusual and pigmented macrophages were not seen. There was no evidence of Aschoff bodies, fibrinoid necrosis, or verrucose angeitis, nor of parasitic infestation.

Coronary Arteries. No abnormalities have been seen in the major coronary vessels but, where the endocardial fibrosis was extremely advanced, obliterative changes were sometimes seen in the smaller vessels.

Histopathology of Valves and Atria

Valvular Apparatus. Abnormalities were only found in the atrioventricular valves with one exception in which there was some thickening of an aortic cusp. The papillary muscles showed the same changes as in the ventricular walls, save that replacement of the muscle fibres by fibrous tissue was commonly more severe. Sometimes the papillary muscle was found to have become a cone of pure white fibrous tissue. The thickening of the chordæ was due to an increase of fibrous tissue on the surface; the deeper portion was cemented to the mural endocardium by organizing fibrous tissue. The valve cusps were similarly affected, being sealed to the mural endocardium by organizing fibrous tissue with deposition of fibrous tissue on their surface.

The characteristic vegetations of a bacterial endocarditis were found on cusps and chordæ in 5 of the 23 damaged mitral valves. Two of the thrombi in the right auricle had become terminally infected. One case had extensive bacterial endocarditis super-imposed on a patch of left ventricular endocardial fibrosis.

Atria. The myocardial changes described in the ventricular walls were also found in the atria, but often extending through the whole thickness of the muscle; such changes were seen in the absence of endocardial changes. Adherent organizing thrombus commonly filled the interstices of the musculi pectinatæ of the right atrium and occasionally covered the smooth muscle layer in the left atrium. Endocardial fibrosis was less frequently seen in the atria as compared with the ventricles and when present was smaller but might still show a granulation tissue layer.

To summarize, there is fibrosis of the endocardium often with thrombus formation, and underneath this fibrous tissue is a vascular layer with a few chronic inflammatory cells. Fibrous bands invade the myocardium, particularly in relation to thin-walled blood vessels. There is atrophy and degeneration of muscle especially in the sub-endocardial region. No arterial occlusion or parasitic invasion is seen, nor is there any clear evidence of infection.

Extra-cardiac Pathology

Study of the extra-cardiac lesions in these necropsies has thrown no light on the cardiac condition. A variety of lesions was seen that might be found amongst any thirty necropsies at Mulago Hospital. Pyelo-nephritis, nephritis, or some renal scarring was present in five cases. Septic renal and splenic infarcts were found in the organs of a patient who had died of bacterial endocarditis; but apart from this and one old infarct in a spleen, infarction was not seen. Two spleens showed nodules of uncertain ætiology of a type often found in Africans. Sickling of the red blood corpuscles was seen at necropsy in three cases only. Active tuberculosis was found in two cases and pneumonia in seven. Cirrhosis was present in four and an excess of periportal fibrous tissue was present in the livers of the others. The adrenals, thyroid, and pituitary glands were usually atrophic by European standards, but these findings, as well as liver fibrosis, are common in Uganda Africans. Subcutaneous œdema was almost invariable and often there were large serous effusions. Syphilis was no more frequent than it is in other patients and was specifically excluded in many. Lesions due to past malnutrition were common, but no more than in other Africans in this hospital.

In summary, the only lesions commonly observed outside the heart were those of congestive cardiac failure and terminal infections.

Summary of Clinical Findings

The clinical picture has been found, not unexpectedly, to depend on the site of the major lesion (Table I). When this is in the left ventricular endocardium, left and right heart failure appear without murmurs or other distinguishing features; diagnosis can be made only by exclusion. When the left ventricular lesion is more advanced, the mitral valve is involved and mitral incompetence results. This is the most easily diagnosed form of endomyocardial fibrosis and probably the commonest. These patients have a loud, commonly high-pitched, apical systolic murmur and thrill, and a moderately enlarged left atrium which may show systolic expansion.

When the main lesion is in the right ventricle the patient develops ascites and œdema without dyspnœa, and is found to have a loud third heart sound but no murmurs. When the tricuspid valve is involved in the fibrosis, the signs of tricuspid incompetence are added. Combinations of these clinical patterns are often seen. A detailed description of the clinical picture was the subject of an earlier paper (Ball *et al.*, 1954).

Cause of Death. Thirteen patients died as a direct result of their endomyocardial fibrosis; eight from heart failure alone, four with heart failure and bacterial endocarditis, and one from bacterial endocarditis alone. Ten patients died from intercurrent infection (pneumonia in six) during the course of chronic heart failure. The remaining six died from various causes, but without any obvious signs or symptoms of heart disease. Three of these had such advanced lesions, both macroscopically in the left ventricular endocardium and the mitral valve and microscopically in the muscle fibres, that it is difficult to understand why gross heart failure had not followed.

Pathogenesis

The provocative agent or agents and the site and character of the initial lesions in this disease are alike unknown. Possible ætiological factors have been discussed elsewhere (Williams *et al.*, 1954). It is clear, however, that there is no great loss of muscle tissue such as would follow severe necrosis of muscle, and the presence of a granulation tissue layer indicates that a process of organization has been going on. It is difficult to believe that this could be anything else but the organization of thrombotic material such as can sometimes be seen in progress in the centre of a nodule of fibrous tissue. Such a process is more commonly seen in the atria. Thrombosis in the ventricles is seen to be more frequently superimposed on the mural surface of an extensive fibrous plaque. It seems likely, therefore, that thrombosis occurs in two stages, at an early stage and at a much later stage as a result of ventricular immobilization. This indication of a vicious circle fits in with the slow inexorable nature of the disease. One probable effect of the endocardial thrombosis and fibrosis is obstruction of the thebesian and arterio-luminal vessels, and dilatation of these vessels is a feature of the histological picture. If such obstruction does develop, and this may be a crucial factor, the lesion will be self-aggravating, the hypoxia of obstruction adding its insult to the injuries already received by the myocardium.

If thrombosis is the factor that initiates the endocardial fibrosis, one must ask what could have caused the mural thrombus. It is generally held that mural thrombus will only be deposited on abnormal endocardium, and with this we agree. In what way could such initial endocardial damage be produced? It might be the result of some direct injury. The relative delicacy of the endocardium of the inflow tract (Nagayo, 1909) the region predominantly involved, suggests that some factor operates directly on the inflow tract endocardium that spares the coarser outflow tract endocardium. Direct mechanical injury to the endocardium has been held responsible for the fibrotic patches of endocardium associated with congenital defects (Taussig and Semans, 1940) and with valvular incompetence (Schmincke, 1908; Saphir, 1930); but there is no evidence that such

factors are operating in endomyocardial fibrosis, save perhaps in some of the left atrial lesions associated with mitral incompetence.

Alternatively the endocardium could be damaged as a result of spread from an initial myocardial lesion. Support for this view comes from the existence of lesions in the subendocardial muscle in chambers and regions that show no endocardial fibrosis, as well as in those that do. Another supporting observation is that in the valves, where the endocardium is not in contact with the heart wall, isolated lesions are not seen; valvular fibrosis is always in continuity with lesions of the adjacent mural endocardium.

It seems likely, therefore, that the sequence of events is as follows: initial damage to the subendocardial muscle, spread of process to the endocardium, primary mural thrombosis, organization of the thrombus to fibrous tissue, obstruction of communicating vessels by thrombus and fibrous tissue causing increased myocardial damage, and finally secondary mural thrombus when the fibrotic lesion is extensive. It is not suggested that this chain of events is complete or that it is proved, and there are certain puzzling discrepancies.

One feature of our cases has been the extraordinary infrequency with which embolic lesions have been encountered, despite much mural thrombosis, even in late cases. If mural thrombosis is an early lesion, we can only suppose that the thrombi become speedily and firmly attached and perhaps because of the lack of cardiac hypertrophy, the feebleness of the heart's action, or because of the rapidity with which endothelium can grow over fibrin thrombi (Duguid, 1949), they are infrequently dislodged. Our search for early cases in acute heart failure or in accidental deaths has not so far revealed evidence of the squence of changes we have postulated. While mural thrombosis has been reported in South Africa to be frequent (Higginson *et al.*, 1952), the lesions of advanced endomyocardial fibrosis are very rare (Gillanders, 1954).

Discussion

The recurring pattern of lesions that we have encountered in these hearts fits into none of the accepted varieties of heart disease. In reviewing the literature we find reports of some conditions that are very similar; they would, indeed, have been accepted by us on our criteria of selection, " the presence of mural endocardial fibrosis, easily visible to the naked eye and due to none of the recognized causes." This does not of course presuppose pathogenetic or ætiological identity. We are reviewing these reports under three headings.

(1) *Reports of Hearts Closely Similar to Endomyocardial Fibrosis*

These reports fall into two groups—those reported from Africa, and those from Europe and America, the latter mainly reports of isolated or small groups of cases.

African Cases. Bedford and Konstam (1946) described 40 cases of unexplained heart failure in East and West African soldiers, and in 17 necropsied cases they report " some had an obvious and extensive subendocardial fibrosis . . . adherent to which was organized ante-mortem clot." O'Brien (1954) has described 25 patients with heart failure from the Sudan with necropsy evidence of endomyocardial fibrosis in two; in one of these there was involvment of the tricuspid valve such as we have described.

Personal communications have revealed that similar cases are fairly common in Southern Rhodesia (Gelfand, 1954) and Northern Rhodesia (Buck, 1954). Reports of three white patients who contracted the disease have come from West Africa (Edge, 1946; Gray, 1951) and one of us has seen a typical case there, in an African from the Gambia. Although we have not full details about many of these cases, there is strong cumulative evidence that the disease is widespread in Africa.

Non-African Cases. From outside Africa have come a small number of case reports, mainly from the United States and from Switzerland. American reports include those of Smith and Furth (5 cases, 1943), McNicol *et al.* (2 cases, 1953), Fienberg and Holzmann (1951), and McKusick

and Cochran (1952). In the last two reports there was striking obliteration of the right ventricle, close in its resemblance to the lesion we have described.

The reports from the European continent have come mainly from Switzerland. In 1936 Löffler described two patients with extensive endocardial fibrosis: both had a high blood eosinophilia. Somewhat similar cases, sometimes without the eosinophilia, have been described from Switzerland (Egger, 1944; Roulet, 1944; and Berblinger, 1948); from Germany (Mumme, 1940); from France (Landau *et al.*, 1927; Lenègre and Gerbaux, 1952); and from Austria (Fossel, 1942). The identity of these lesions with each other and with endomyocardial fibrosis is not easy to establish, and the significance of the eosinophilia is not certain. In some of the Swiss cases it disappeared during certain stages of the disease. It was common but not constant in our Uganda cases, but some of these had helminthic infestations capable of causing high degrees of eosinophilia. Personal conversations with Swiss colleagues has shown that they have doubts as to Löffler's disease and endomyocardial fibrosis being identical diseases. Pending further observations, we therefore reserve judgment on this matter.

(2) *Reports of Hearts that Show only Some Similarity to Endomyocardial Fibrosis*

Certain conditions have been reported from other parts of the tropics in which the cardiac abnormalities include mural thrombus and some degenerative myocardial lesion. A slight degree of endocardial fibrosis, usually beneath the thrombus, is present in some. Normet (1937) in his description of the lesions in the disease which had been called Bouffissure d'Annam, and which is now thought to be adult kwashiorkor (Trowell *et al.*, 1954), described mural thrombosis of the ventricles with vacuolation of the myocardial fibres but without fibrosis. It was seen in patients with fatty livers and with atrophic pancreatic lesions. The disease described from South Africa by Gillanders and his associates (Gillanders, 1951; Higginson *et al.*, 1952) was also seen in patients who had liver disease presumed to be due to malnutrition. Their descriptions of the changes in the myocardial fibres are similar to those we have described; there was marked mural thrombosis, in some cases with minor degrees of subjacent fibrosis. Embolic phenomena were common and severe degrees of endocardial fibrosis with valvular involvement were not seen. It is possible that these were severe early manifestations of a process that develops more slowly and silently to severe fibrosis in Uganda Africans. We have seen similar cases to these in Uganda (Davies, 1950), but as previously remarked there are some obscurities which further observations may resolve. In Uganda embolic phenomena are very unusual and severe liver disease, while often present, is not so evident as in the South African natives.

The report of Becker *et al.* (1953) is not easy to evaluate. They do not refer to the cases described by Gillanders. They have reported a heterogenous group of patients, of different races, who died of heart failure with mural thrombosis in the ventricles. There was little evidence of fibrosis and no mention of valvular lesions. From their studies, and from the use of histochemical methods, they concluded that they were dealing with a cardiac collagenosis. We would interpret their findings rather differently and can see nothing in our own specimens to suggest that they fall into the collagenosis group.

The cases of mural thrombosis in South Africans and in Annamites may well be related to endomyocardial fibrosis, but we think it is premature to insist at this stage that there is an association.

(3) *Reports of Cardiac Conditions that though Distinct Show Endocardial Fibrosis of some kind*

Congenital Endocardial Fibroelastosis. This condition is predominantly a disease of early childhood (Craig, 1949; Gowing, 1953), but can also occur in adults, and most writers believe that it is congenital in origin. Macroscopically there are certain resemblances to endomyocardial fibrosis but aortic and pulmonary valve lesions are common and the process is one that predominantly involves the out-flow tract endocardium.

Histologically there are distinct differences, as has been shown by Thomas *et al.* (1954). In

endomyocardial fibrosis there is a lack of the characteristic elastosis, thrombosis seems to be an integral part of the lesion, and there is evidence of a destructive type of lesion rather than a proliferative lesion such as is seen in fibroelastosis. In both diseases it seems that the thickened endocardium obstructs the arterio-lluminal circulation (Weinberg and Himmelfarb, 1943).

Rheumatic Carditis. This condition is not uncommon in Africans and, pathologically at least, it resembles the disease as seen in Europe. The endocardial fibrosis is usually confined to the valves but it may spread to involve to a minor degree the mural endocardium, particularly in the left atrium and ventricle. In endomyocardial fibrosis, the spread is in the reverse direction, from the mural endocardium to the valve. The mitral lesions of one disease can to some extent mimic those of the other disease, especially those rheumatic valves showing pure incompetence and the "endomyocardial" valves showing stenosis. The aortic valve, so frequently affected in rheumatism is rarely affected in endomyocardial fibrosis. No histological evidence of past or present Aschoff bodies has been found in endomyocardial fibrosis. The two diseases would seem to resemble each other in the slow relentless progression of the fibrosis, and the mechanism of fibrin deposition on a damaged surface described by Magarey (1951) may well operate in both diseases.

Ischæmic Heart Disease. Cardiac infarction may heal with endocardial scarring, but in endomyocardial fibrosis no lesions have been found in the major coronary arteries, and the distribution of the endocardial and of the myocardial fibrosis is unlike that found to result from cardiac infarction. The subendocardial distribution of the muscle lesions recalls the acute coronary insufficiency of severe anæmia (Master *et al.*, 1950) but anæmia has not been marked in our cases nor has it figured prominently in their past histories. The possible effects of the endocardial fibrosis and thrombosis on the arterio-luminal vessels has been mentioned. An isolated patient with extensive endocardial fibrosis associated with multiple infarcts was recently described (Hughes and Smith, 1953).

Diffuse Collagen Diseases. The cardiac lesions that have been described in diffuse lupus erythematosus (Gross, 1940) and scleroderma (Weiss *et al.*, 1943; East and Oram, 1947) sometimes show a slight degree of fibrosis extending to the endocardium, but the myocardial fibrosis predominates. A recent African patient with scleroderma heart disease showed lesions no different from those reported in Europeans.

Virus Myocarditis. Although many viruses are known to cause myocarditis in man (Saphir, 1953; Lyon, 1947) the endocardium is not particularly attacked. In rabbits myxoma virus causes a myocarditis in which there is "striking thickening of the endocardium of the ventricles with obliteration of all the crevices between the trabeculæ" (Pearce, 1954). Other experimental virus infections cause thickening of valve cusps and myocardial calcification (Pearce, 1950). Whether viruses can produce such lesions in man is not known, but they point to the possibility that virus infection may be an ætiologic factor in endomyocardial fibrosis.

Heart Disease from Malnutrition. One or two reports suggest that malnutrition may be responsible for endocardial fibrosis (Smith and Furth, 1943; Brinkman and Prior, 1950). There are many nutritional disorders in man and animals that can cause myocardial lesions, but endocardial fibrosis is a feature in none. Prominent among these is beri-beri, which is exceptionally rare in Uganda, and our patients with endomyocardial fibrosis have shown no response to vitamin B1. The conditions described in South Africa and Annam have been mentioned above.

Comment. This review of the different types of endocardial fibrosis indicates that virus infection, some antigen-antibody reaction, and malnutrition are possible ætiological factors in the form of endocardial fibrosis common in Uganda.

Summary

Endomyocardial fibrosis is one of the commonest causes of heart failure in Africans in Uganda. A description of the pathology, macroscopic and microscopic, is given, based on a series of 32 necropsies.

The lesions of the left heart consist essentially of fibrosis of the endocardium and underlying myocardium at or near the ventricular apex. Thrombus is commonly deposited on the surface of the abnormal endocardium and calcification is not infrequent in its depths. This fibrous tissue tends to spread up to involve the papillary muscles, chordæ, and cusps of the mitral valve; the process is particularly liable to involve and immobilize the posterior mitral cusp. Incompetence is the usual result of the mitral lesion; stenosis follows occasionally. Bacterial endocarditis of this valve is not uncommon terminally. The left atrial endocardium sometimes shows small patches of fibrosis.

The right heart lesions are in general similar to those on the left. Ventricular endocardial fibrosis is as constant as it is on the left, but usually the lesions are less extensive. When the fibrosis does extend to involve more than one-third of the ventricle it produces an obliteration of the in-flow tract which has no parallel on the left side. The tricuspid valve lesion is similar to the mitral but less extensive. It also produces incompetence and occasionally stenosis. The right atrium commonly contains ante-mortem thrombus; some of the small fibrotic patches of the atrial endocardium are directly connected with organizing thrombus.

Histological studies show massive thickening of the endocardium, the major part of which consists of acellular fibrous tissue; the deepest layer contains many small blood vessels with some chronic inflammatory cells. Strands of fibrous tissue penetrate the myocardium to a varying depth. Degenerative changes are nearly always present in the myocardial fibres even in regions and chambers that show no endocardial lesions.

No significant lesions are found outside the heart, except for those resulting from heart failure or terminal infection.

The clinical features and the cause of death are briefly reviewed.

The nature of the pathogenesis is discussed, and reasons are given for thinking that the lesion may start in the sub-endocardial muscle with subsequent spread to the endocardium. The causative agent is unknown. Organization of thrombus is thought to play an important part in the development of the massive fibrosis.

Reports of similar conditions occurring in Africa, North America, and Europe are surveyed. The other causes of fibrosis of the endocardium are also briefly reviewed.

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PHONOCARDIOGRAPHY IN ACUTE RHEUMATIC CARDITIS

BY

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The diagnosis of early rheumatic carditis usually depends upon the detection of murmurs produced by acute valvulitis. It may be difficult to evaluate clinically the significance of certain murmurs occurring in patients with rheumatic fever, though the development of a loud apical pansystolic murmur in a patient already under observation usually presents no diagnostic problem. More frequently a systolic murmur is present when the patient is first seen: then the distinction between systolic murmurs of basal and of mitral origin may be difficult, and in the presence of fever, pain, and resultant tachycardia, it may be impossible to ascertain the significance of the murmur by auscultation alone. The undoubted presence of a mitral diastolic murmur is diagnostic of mitral valvulitis, but the faint short diastolic murmur that first appears is readily confused with a loud third sound or summation gallop, and the clinical distinction between diastolic sounds and murmurs may be uncertain. Similarly it may be difficult to be sure of the presence of the soft aortic diastolic " whiff " of acute aortic valvulitis. It was therefore decided to investigate these murmurs by phonocardiography.

There have been very few reports of the phonocardiographic findings in acute rheumatic carditis. The mitral diastolic murmurs of acute valvulitis have been recorded by Schwarzchild and Feltenstein (1934), Johnston (1935), and McKee (1938). Taquini *et al.* (1940) investigated the mitral murmurs in a small group of patients with acute carditis: they concluded that the diastolic murmur they had diagnosed clinically in nine cases was due either to summation or near summation of the third and atrial sounds, or else that it was caused by prolongation of the third sound and was not therefore a true murmur. Tachycardia rendered interpretation difficult in some of their cases: although those phonocardiograms recorded at a slower heart rate are of small amplitude, a true diastolic murmur appears to be present in one of these tracings.

Frequencies of Murmurs

Before starting this work a rough analysis was made of the frequencies of the murmurs of acute rheumatic carditis using an audio-frequency spectrometer. This instrument incorporated 27 band-pass filters set between frequencies of 40 cycles/sec. and 16 kilocycles/sec. Each filter was allocated a specified horizontal position for a beam on the screen of a large cathode-ray tube. The beam traced a vertical line at each of the 27 positions, and the height of each vertical deflection indicated the intensity of sound in that particular range. It was not possible to analyse separate phases of the cardiac cycle; therefore the intensity of the sounds and murmurs in one full cycle was determined. The lower graph in Fig. 1 and the cross-hatched area of the upper graph were derived from the findings at the mitral area in eight normal children, and the remainder of the upper graph represents the intensities of sound at each frequency in twelve children with mitral valvulitis. A statistical analysis was made of the differences between the mean values of intensity at each frequency in the normal and abnormal groups. Values for " t " were computed and probability of the differences being due to chance was assessed ($P = <0{\cdot}01$). In the case of the mitral murmurs a significant difference was shown between frequencies of 80 and 1600 cycles/sec. Similar results were obtained in the analysis of aortic murmurs. The amplifier used for this investigation had insufficient power to amplify the high frequency murmurs of low intensity, and it was thought that such murmurs might well occupy

frequencies higher than 1600 cycles/sec. Therefore it was considered desirable to employ a phonocardiograph that would provide adequate records of murmurs composed of frequencies up to 2000 cycles/sec. For this reason a cathode-ray apparatus was designed, the first model of which has already been described (Besterman and Harrison, 1953).

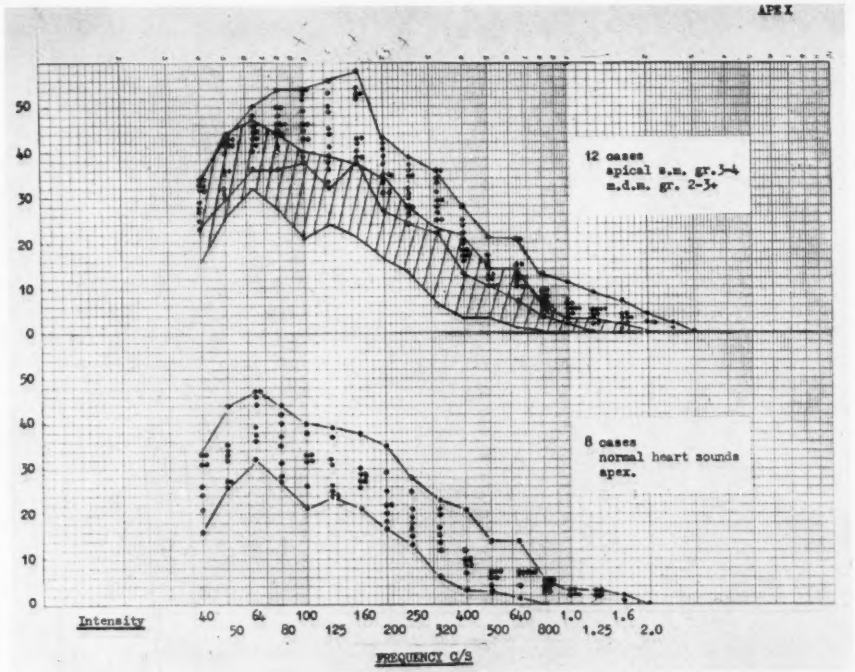

FIG. 1.—Lower graph. Intensity of heart sounds between frequencies of 40 and 2,000 cycles/sec. recorded from the mitral area in eight normal children. Upper graph. Intensity of sounds and murmurs at the mitral area in 12 children with acute mitral valvulitis similarly determined by the audiofrequency spectrometre and superimposed on the normal range (cross hatched area).

Calibration of amplification was provided by the introduction of a 50-cycle signal on to the record of each amplifier. The excursion of this signal was proportional to the amount of gain used in recording on each channel.

The following account concerns the results obtained with this early model in 230 children treated at the Special Unit between 1950 and 1952. Since that time, the original phonocardiograph has been modified and these later recordings form the basis of a more detailed investigation of the murmurs that is being conducted at present.

METHOD

In the present study murmurs were graded clinically from one to four according to intensity. The phonocardiograms illustrated in this paper were recorded simultaneously with an electrocardiogram, SL. 2. The site of the microphones is represented by the initials MA or LSE, indicating mitral area, and left sternal edge in the third and fourth left interspace. Low, medium, or high pass filters are abbreviated as L.F., M.F., and H.F. respectively. In some phonocardiograms, simultaneous mitral recordings were made using different filters (Fig. 2). Serial records were obtained with the patient lying in the same position, and the microphones placed at identical sites. The degree of amplification was calibrated in some of these phonocardiograms (Fig. 7, 12, and 13).

Heart Sounds

In patients with early rheumatic carditis no abnormality of the atrial, first, or second heart sounds was detected by phonocardiography. The first heart sound was not accentuated, and no opening snap was ever recorded in these cases.

The third heart sound is detected in normal children more frequently than in adults. In 1951 a preliminary analysis of our phonocardiograms showed accentuation of the third sound in many children with mitral incompetence (Fig. 2). Although we were not then aware that this accentuation

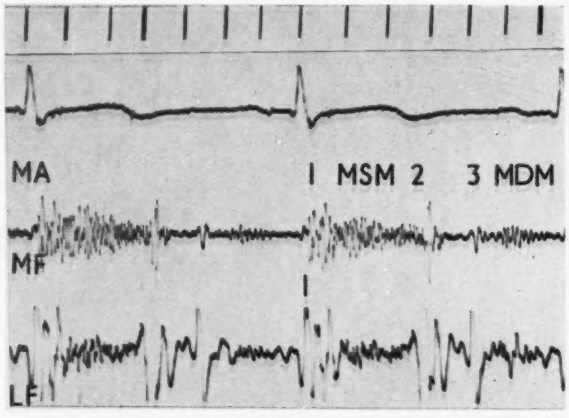

Fig. 2.—Acute rheumatic mitral incompetence with a pansystolic murmur and an accentuated third heart sound initiating a short mitral diastolic murmur.

had been previously described, we have since found that Bouillaud (1835) noted an extra sound in a patient with acute carditis and an apical systolic murmur; and that Coombs (1924) and Sprague and White (1926) had noted a loud third sound in children with mitral incompetence.

This sign had probably been overlooked by us previously as the third heart sound commonly initiated a mitral diastolic murmur of similar frequency with which the sound could have been easily confused on auscultation. Once attention had been drawn to accentuation of the third sound on the phonocardiogram, the louder sound was detected clinically in many patients with mitral incompetence, and proved to be a helpful sign in the diagnosis of this valve lesion.

Subsequently Brigden and Leatham (1953) have described an audible third sound in 50 per cent of 30 adults suffering from pure mitral incompetence; and further confirmation has been provided by Wood (1954) who noted this sound in 85 per cent of patients with well developed incompetence.

It is presumed that the accentuation of the third heart sound in mitral incompetence is due to the increased rate of early ventricular diastolic filling.

Systolic Murmurs

In 1830 Elliotson described a bellows murmur associated with acute endocarditis: at necropsy he noted deformities of the mitral valve which he considered sufficient to have caused mitral regurgitation. Hope (1839) stated that in 1831 he had been the first to appreciate the diagnostic significance of murmurs in rheumatic heart disease. He believed that mitral regurgitation was the most important lesion of early rheumatic carditis and described the characteristic features of the systolic

murmur; these included maximum intensity at the apex, loudness, and early onset often concealing the first heart sound. Disagreement still exists concerning the mechanism by which the valve becomes incompetent. Dilatation of the ventricle and valve ring has been invoked to explain this lesion by Owen (1886), Sturges (1894), and Thayer (1925). The other view that inflammation and swelling of the cusps prevent proper closure of the valve, thus allowing regurgitation of blood during systole, was advanced by Todd (1849), and Cheadle (1889); and both Coombs (1924) and Levine (1945) have agreed that this may be the mechanism by which incompetence is produced in early carditis. Besterman and Thomas (1953) have shown that cardiac enlargement does not occur in early acute rheumatic heart disease, and we believe that acute valvulitis alone causes mitral incompetence in these cases. However, cardiac enlargement and dilatation of the mitral ring are usually found in cases of established mitral incompetence.

A basal systolic murmur is commonly present in normal children, usually of maximum intensity in the pulmonary area, and frequently conducted to the apex. An innocent murmur was detected in the mitral area in 90 per cent of normal children by McKee (1938); and if tachycardia is present it may be difficult to distinguish from an organic mitral murmur. In 1846 Barlow observed the fundamental distinction between systolic murmurs of basal and mitral origin according to their duration in systole. Using the phonocardiograph, Lian and Racine in 1933 described the pansystolic duration of the mitral murmur (Fig. 2) and this characteristic has subsequently been confirmed by Cossio (1937) and Leatham (1951). By contrast, organic basal systolic murmurs, whether of pulmonary or aortic origin, reach maximum intensity in mid-systole and end before the second sound (Lewis, 1915; Castro *et al.*, 1947; and Leatham, 1951 and 1952). " Innocent " or " benign " basal systolic murmurs are of similar character, but usually softer, of grade one or two intensity, and may be early or delayed in onset (Fig. 3).

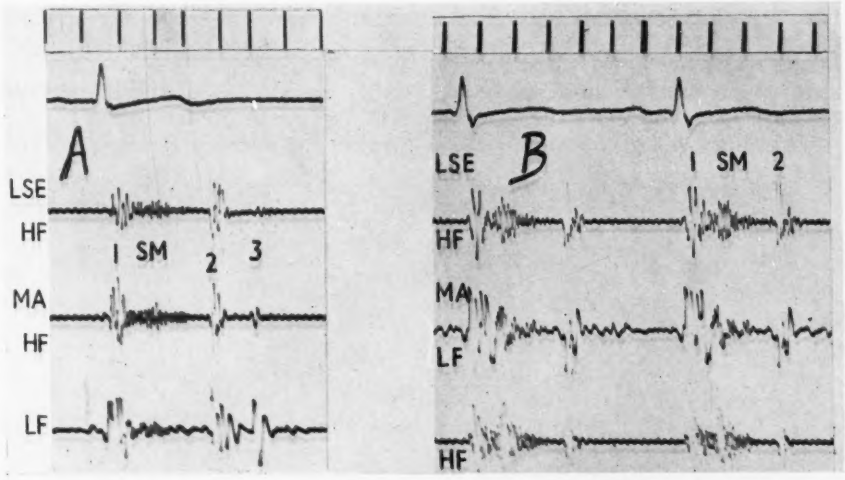

FIG. 3.—Recordings of benign basal systolic murmurs conducted to the mitral area; (A) early onset, (B) delayed onset.

In acute rheumatic carditis phonocardiography is of particular value in assessing the duration, and therefore the significance, of systolic murmurs in the mitral area. This application of the phonocardiogram is illustrated by Fig. 4A. The patient had signs of established aortic valve disease, without cardiac enlargement, together with an apical systolic murmur of uncertain origin: a pre-

systolic murmur was also present, possibly due either to an Austin Flint effect, or else to mitral valvulitis. The phonocardiogram demonstrated a distinct pansystolic mitral murmur. Recovery ensued, and the signs of mitral valvulitis disappeared, leaving only the murmurs of established aortic valve disease (Fig. 4B). In this patient a second attack of rheumatic fever had been accompanied by transient mitral valvulitis as evidence of further carditis: this knowledge was only conclusively provided by the phonocardiogram.

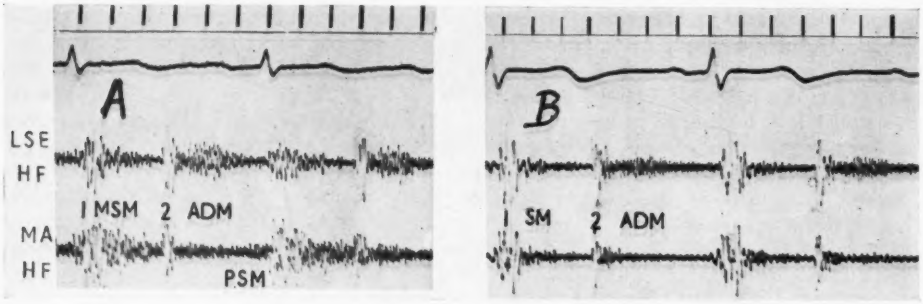

FIG. 4.—(A) Second attack of rheumatic carditis: phonocardiogram showing murmurs of aortic incompetence and acute mitral valvulitis. (B) Disappearance of mitral and persistence of aortic murmurs.

The development of a mitral systolic murmur usually occurs early in the course of acute carditis, often preceding admission to hospital, and is observed only infrequently. Fig. 5A was recorded from a patient with acute rheumatic pericarditis without evidence of valvulitis. A recurrence of rheumatic activity occurred during convalescence and mitral incompetence developed under observation (Fig. 5B).

In some patients with mitral pansystolic murmurs the murmur was most intense in late systole. Fig. 6 demonstrates the usual mitral systolic murmur which was of grade 3 intensity, and the subsequent change when it showed late systolic accentuation, and its eventual disappearance, leaving

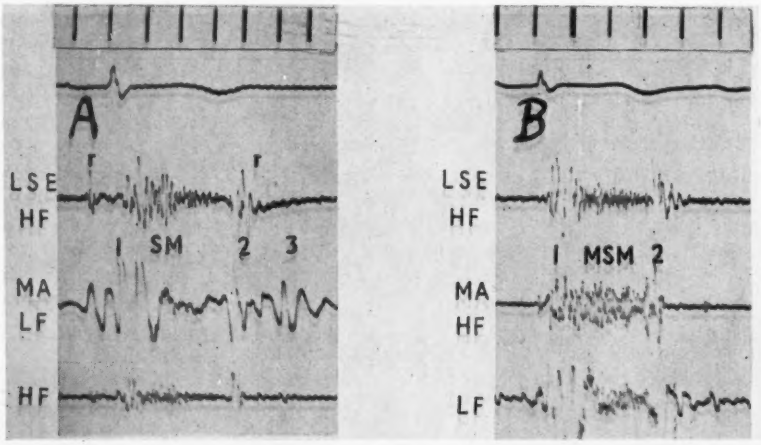

FIG. 5.—(A) Acute rhuematic pericarditis with a basal systolic murmur; (B) Subsequent recurrence of rheumatic carditis with development of a pansystolic mitral murmur.

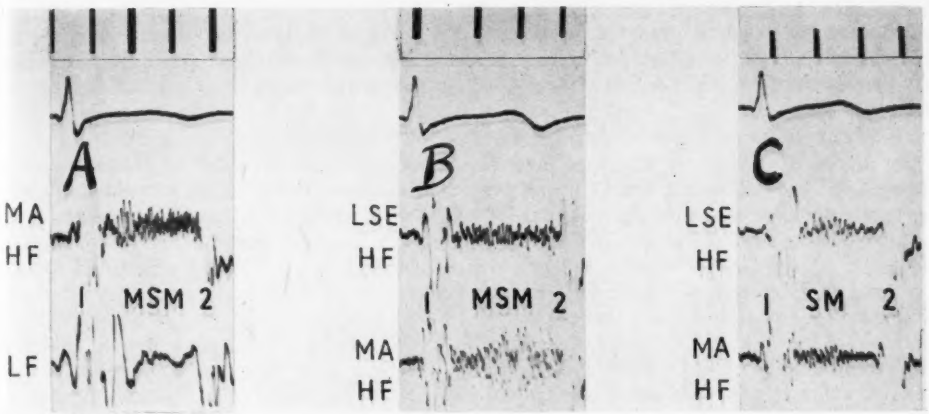

FIG. 6.—Serial recordings from one patient showing (A) pansystolic mitral murmur, (B) late systolic accentuation of this murmur and (C) disappearance of the mitral and persistence of a midsystolic basal murmur.

only a mid-systolic murmur at the mitral area, presumably of basal origin. Phonocardiograms of mitral late systolic murmurs invariably demonstrated the pansystolic duration of the murmurs although clinically they may have been sufficiently faint in early systole to be inaudible in this phase. Occasionally late systolic murmurs may occur in the absence of organic heart disease; in the few examples studied the phonocardiogram showed no vibrations in early systole.

Complete recovery from mitral valvulitis may occur. Fig. 7A was recorded from a nine-year-old girl three weeks after the onset of her first attack of rheumatic fever: mitral systolic and diastolic murmurs were heard, and there was left atrial enlargement due to the mitral incompetence, but no generalized cardiac enlargement. Two weeks later complete clinical and radiological recovery had occurred, and the phonocardiogram (Fig. 7B) no longer showed mitral systolic and diastolic

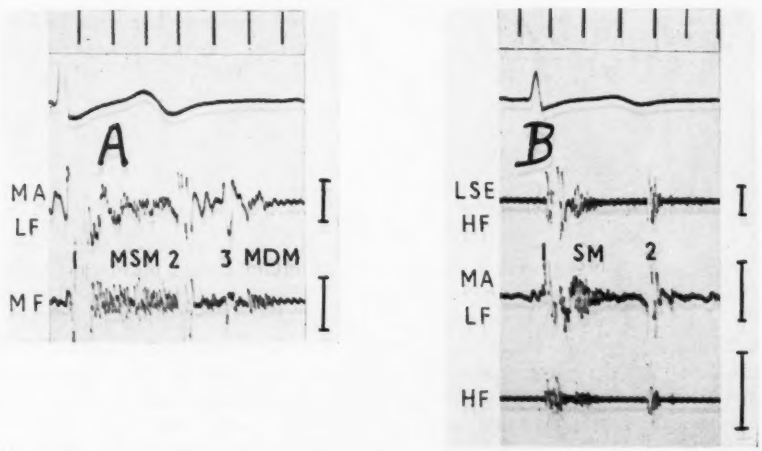

FIG. 7.—(A) Acute mitral valvulitis of three weeks duration, with mitral pansystolic and diastolic murmurs. (B) Recovery, no significant mitral murmurs detected.

murmurs, but only a benign basal systolic murmur conducted to the mitral area. The degree of amplification used in these two phonocardiograms is indicated at the side of each tracing.

In patients with mitral valvulitis, systolic murmurs alone were rarely observed; diastolic murmurs were detected in addition to the systolic murmurs in 93 per cent of these patients.

Mitral Diastolic Murmurs

The earliest description of the apical diastolic murmur in acute carditis occurs in a case history cited by Bouillaud (1835). In a patient first seen on November 24, 1833, a systolic murmur and an extra sound were audible at the apex; by early December the signs had altered, and were described as " ticss . . . tac . . . tac . . . sss ". Thus an apical diastolic murmur was noted to develop, following a (?) third heart sound. In 1892 Sturges recognized that this murmur could occur in the absence of mitral stenosis, and that it might appear to be presystolic in timing in the presence of tachycardia. Coombs described the murmur in 1907 and in subsequent papers he noted that it was transient in some cases. In 1924 Coombs stated that the murmur was probably caused by acute valvulitis in cases of early rheumatic carditis. The cause of the murmur is still disputed: Bland and Jones (1952) considered that it might be due to relative mitral stenosis, but left ventricular enlargement is not present in early carditis at a time when this murmur is often first detected. Fishberg (1940) and Wood (1950) supported the valvulitis theory and noted the absence of diastolic murmurs in patients with cardiac enlargement of other ætiologies. Inflammation diminishes the flexibility of the valve cusps and gives rise to vegetations. These stiffened cusps and the surface irregularities set up eddy currents during the phase of rapid ventricular filling and cause the mitral diastolic murmur. With a slow heart rate the rapid-filling phase follows the third heart sound (Fig. 7A); during tachycardia it many occur during atrial systole (Fig. 8A).

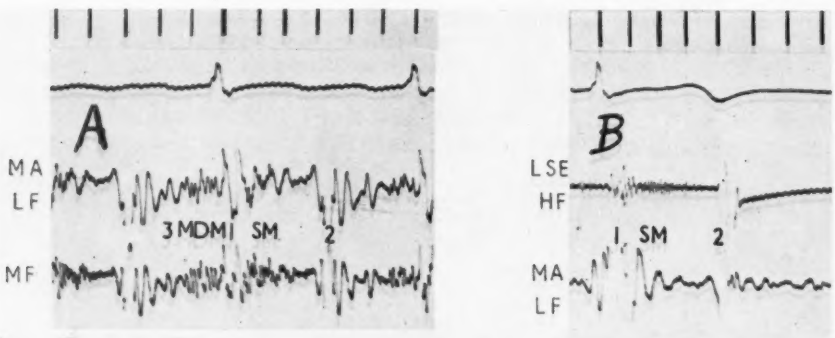

Fig. 8.—(A) Mitral diastolic murmur of acute caditis occurring during atrial systole in the presence of tachycardia. (B) Subsequent disappearance of mitral murmur.

The murmur may be clinically confused with a loud third heart sound owing to their similar pitch. The third sound usually occupies a frequency of 20–60 cycles/sec. and the murmur one of 40–100 cycles/sec. Thus in some cases a low-pass filter will demonstrate the third sound and murmur equally well (Fig. 2); but if the murmur occupies the higher range of frequencies a medium-pass filter shows the murmur better than the third sound (Fig. 7A). The duration of the third sound is 0·03–0·06 sec., whereas the diastolic murmur is of greater duration than 0·08 sec. Thus the phonocardiogram is of value in distinguishing between sound and murmur when the difference is clinically uncertain.

These mitral diastolic murmurs often disappeared, but no initial phonocardiographic distinction could be made between the transient and permanent murmurs. The characteristic fluctuating

intensity of these murmurs made repeated observations necessary before it could be ascertained that a murmur had truly disappeared. The increased cardiac output associated with physical acitivity might elicit murmurs that had apparently disappeared during rest in bed. Therefore it was necessary to examine these children after mobilization before deciding that recovery was complete. The disappearance of the typical short mitral diastolic murmur of grade 1 intensity is shown in Fig. 8. In this patient the murmur was never heard subsequently, and complete recovery from carditis occurred.

However, murmurs of greater duration and intensity also proved transient. Fig. 9A was recorded from a patient suffering from mild aortic incompetence and a second attack of rheumatic fever; a long mitral diastolic murmur appeared five days later (Fig. 9B) and persisted for several weeks: no

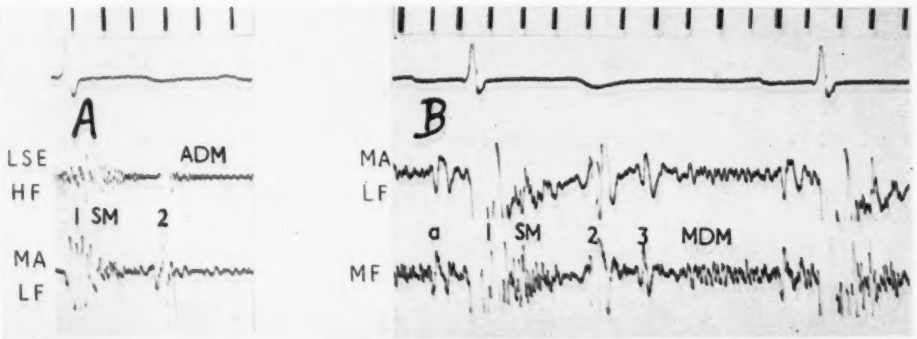

FIG. 9.—(A) Second attack of rheumatic carditis showing aortic diastolic murmur alone. (B) Development of long mitral diastolic murmur five days later.

mitral systolic murmur was detected at any time. The diastolic murmur then disappeared, and at the time of discharge from hospital the cardiac signs were identical with those found on admission.

The mitral diastolic murmur frequently occurred in the absence of a systolic murmur and was often the earliest sign of carditis to be detected. Furthermore, in patients without florid clinical signs, the detection of this murmur helped to confirm the diagnosis of rheumatic fever.

AORTIC DIASTOLIC MURMURS

Stokes (1854) and Walshe (1854) recognized the aortic diastolic murmur as a sign of acute rheumatic carditis. Coombs (1907) pointed out that the murmur occurred without peripheral signs of free aortic regurgitation, that it often first appeared during recovery, and that it was transient in some cases. The murmur is caused by a mild degree of aortic incompetence due to aortic valvulitis. On the phonocardiogram the murmur of established aortic incompetence is initiated by the second sound and is of decrescendo configuration and of long duration (Fig. 10); whereas the softer murmur of early rheumatic valvulitis is of the crescendo-decrescendo form (Fig. 11) described by Wells *et al.* (1949) and Leatham (1950), and is shorter in length. The aortic murmurs of grade 3 and 4 intensity occupy frequencies of 400–800 cycles/sec., whereas the grade 1 and 2 aortic murmurs are frequently of higher pitch and therefore more difficult to record on the phonocardiogram.

Recovery from aortic valvulitis may occur, with disappearance of the diastolic murmur. Fig. 12A was recorded from a patient with an aortic murmur of grade 1 intensity. The murmur was no longer heard during convalescence, even after increased physical activity, and no murmur was demonstrated at this time (Fig. 12B), even using a greater degree of amplification than for recording Fig. 12A.

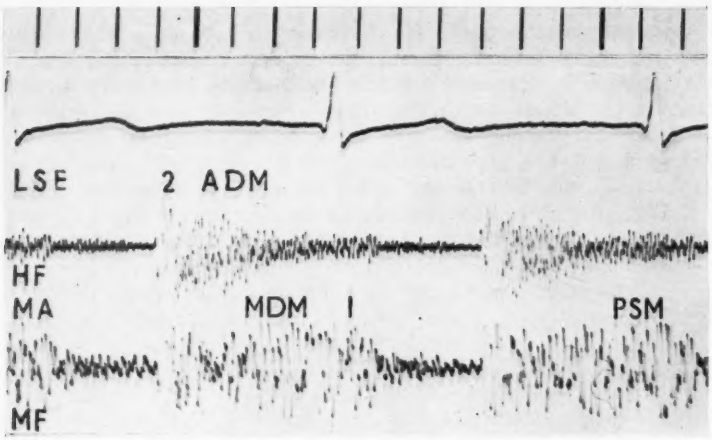

FIG. 10.—Decrescendo murmur of established aortic incompetence.

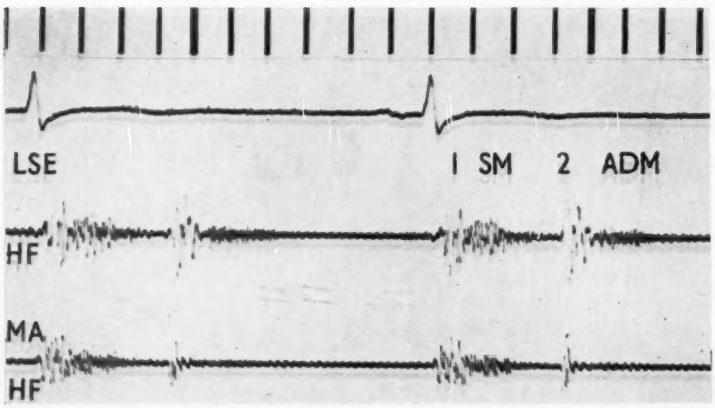

FIG. 11.—"Crescendo-decrescendo" murmur of early acute aortic incompetence.

Pinpoint perforation of an aortic valve cusp may occasionally occur in acute rheumatic carditis and be the cause of the sudden appearance of a grade 4 intensity aortic diastolic murmur (Fig. 13A). Thrombotic occlusion of the perforation presumably accounted for the diminishing intensity of the murmur shown in subsequent records from this patient (Fig. 13, B and C). This change of intensity was confirmed by the increased amplification necessary to record the murmur.

Aortic stenosis is never seen in early rheumatic carditis, and the distinction between basal systolic murmurs of aortic and pulmonary origin has not yet been made by phonocardiography.

PHENYLEPHRINE

Phonocardiography alone may ascertain the presence of faint diastolic murmurs, especially those of mitral origin that may be confused with a third sound clinically. Further clinical con-

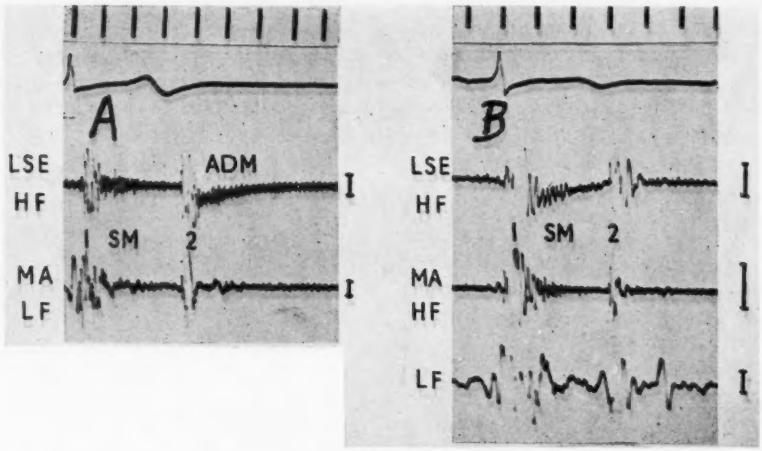

FIG. 12.—(A) Aortic diastolic murmur of grade one intensity in acute carditis. (B) Disappearance of aortic murmur.

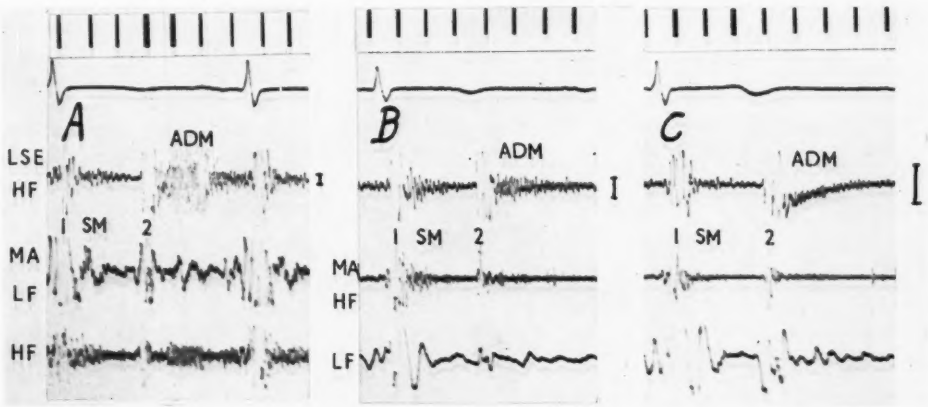

FIG. 13—(A) Aortic diastolic murmur of grade 4 intensity due to perforated aortic valve cusp in acute rhuematic carditis. (B) and (C). Subsequent diminution of intensity murmur, attributed to thrombotic occlusion of the perforation.

firmation can be obtained by the use of intravenous phenylephrine (Besterman, 1951). Phonocardiograms recorded before and after the injection provide a permanent record of the transient accentuation of murmurs produced by the drug. Fig. 14A was obtained from a patient in whom the presence of both diastolic murmurs was doubtful clinically. No definite murmurs were demonstrated either on this phonocardiogram or on another recorded eight days later, but phenylephrine was then injected and mitral and aortic diastolic murmurs of grade-one intensity were clearly shown (Fig. 14B).

Tachycardia alone may mask mitral diastolic murmurs clinically and on the phonocardiogram. Cardiac slowing by carotid sinus pressure may be necessary before the presence of the murmur is verified. Phenylephrine has also been used for this purpose. Fig. 15A was recorded from a nervous child with tachycardia and aortic valvulitis, but a further record (Fig. 15B) showed the aortic diastolic murmur at the left sternal edge and at the mitral area. No distinct mitral diastolic murmur was heard at the apex until the heart rate was slowed by intravenous phenylephrine (Fig. 15C).

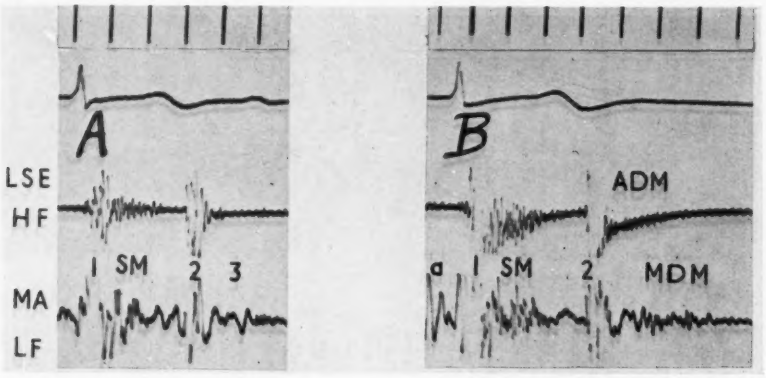

FIG. 14.—(A) Recording from patient with acute rheumatic fever in whom the presence of significant murmurs could not be ascertained. (B) Demonstration of mitral and aortic diastolic murmurs following an injection of phenylephrine intravenously.

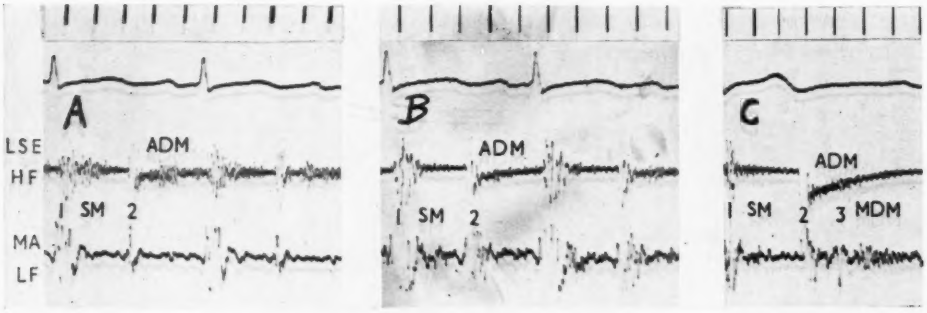

FIG. 15.—(A) Acute aortic valvulitis and tachycardia. (B) With aortic murmur conducted to mitral area. (C) Bradycardia following phenylephrine demonstrates distinct mitral diastolic murmur.

PERICARDITIS

Phonocardiography is rarely necessary to distinguish between rubs and mitral murmurs. Owing to the high pitch of both rubs and aortic diastolic murmurs, these two may occasionally be confused clinically. The distinction may also be difficult to make by phonocardiography, but a diastolic rub may be distinguished from a murmur by the later onset of the rub and the presence of the rub in other phases of the cardiac cycle—atrial and ventricular systole. Fig. 16 illustrates a rub in systole and diastole without murmurs.

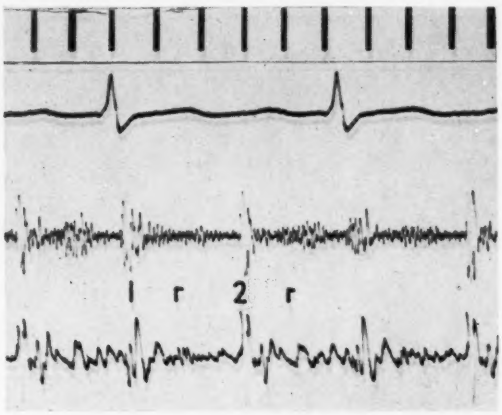

FIG. 16.—Acute rheumatic pericarditis with systolic and diastolic rubs.

SUMMARY

As the diagnosis of rheumatic carditis depends largely on auscultation, phonocardiography has been applied to the study of the murmurs produced by acute valvulitis. When clinical interpretation is uncertain, phonocardiography may aid the initial diagnosis. The duration of a systolic murmur in the mitral area is shown conclusively on the phonocardiogram; the distinction between a short mitral diastolic murmur and a third heart sound may also be made, and the presence of a soft aortic diastolic murmur can be confirmed by phonocardiography.

Phonocardiography provides objective confirmation of auscultatory findings. Such corroboration is of particular value in the study of the changing murmurs of acute rheumatic carditis, and in recording transient accentuation of murmurs induced by phenylephrine. Furthermore, calibration of the amplification employed in serial phonocardiograms provides some evidence of changing intensity of murmurs.

In the present study phonocardiography also drew attention to a clinical sign; accentuation of the third heart sound in mitral incompetence.

In the presence of tachycardia, apical diastolic murmurs cannot always be distinguished on the phonocardiogram. With a normal heart rate the mitral diastolic murmur of Carey Coombs can be readily differentiated from a third heart sound and is a frequent finding in early carditis.

I am indebted to Dr. Paul Wood, Dr. E. G. L. Bywaters, and Dr. Thomas for their helpful criticism and advice; to Mr. J. K. Harrison for technical assistance and to the G.P.O. Research Station, Dolis Hill, for the loan of the audio-frequency spectrometer.

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CONGENITAL AORTIC STENOSIS AND ITS SURGICAL TREATMENT

BY

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The purpose of this paper is to assess the place and timing of surgery in the treatment of aortic stenosis of congenital origin. The diagnosis of aortic stenosis is readily made at the bedside and the clinical features are well known (Levine, 1945; Kiloh, 1950; Campbell and Kauntze, 1953). Its congenital origin is more difficult to substantiate. In the hope of excluding cases of acquired stenosis, we consider here only those patients in whom heart disease was recognized in infancy, or, at latest, on their first routine school medical examination at about five years of age, or in whom the site of stenosis was sub-aortic. Twenty-eight such patients form the basis of this review (Table I): their ages ranged from birth to 25 years. The length of follow-up extended in some instances to ten years and, excluding two infants, averaged nearly four years. Aortic incompetence was also present in six patients and the adult type of coarctation of the aorta in three others. Five patients died as a result of the lesion during the period of follow-up; two in infancy, two before puberty, and one in his middle teens. In six others the stenosis was considered sufficiently severe to justify aortic valvotomy.

Natural History of Aortic Stenosis

The natural history of aortic stenosis is subject to wide variation depending on the severity of the stenosis and the ætiology of the lesion. Acquired aortic stenosis is common both as a result of generalized rheumatic heart disease and as a degenerative state of the aortic valve. The former type is usually recognized from the presence of other valvular flaws, and in the latter type the slow development of the signs of aortic stenosis (Levine, 1949) and the insidious advance of gross cardiac hypertrophy (Dry and Willius, 1939) combine to suggest that the stenosis develops very gradually. The prognosis in rheumatic aortic stenosis follows that of rheumatic heart disease in general and is subject to the same variation. The outlook in degenerative aortic stenosis is good and patients with this lesion may reach old age without disability (Anderson *et al.*, 1952).

Congenital aortic stenosis rarely presents with symptoms and the recognition of heart disease is usually dependent on routine examination performed for some other reason. Congenital lesions with striking signs seldom escape recognition in childhood. In contrast to the soft murmur present early in the course of acquired aortic stenosis, which may be dismissed as benign (Levine, 1949), the basal murmur of congenital stenosis is clearly organic. It may be some years before a thrill in the neck or in the aortic area leads to a precise diagnosis and at first the aortic thrill may be palpable only when the child leans forward with the breath held in expiration. The apical impulse may be normal or may have the typical thrust of left ventricular hypertrophy or may be deceptively abrupt suggesting hypertrophy of the right ventricle; there is no increase of systolic pulsation at the left sternal margin. The first heart sound at the lower left sternal margin and out to the apex is commonly split. The aortic second sound and the pulse pressure are usually within normal limits.

TABLE I

CLINICAL FEATURES IN 28 PATIENTS WITH CONGENITAL AORTIC STENOSIS

Case No.	Sex and age	Age of recognition (years)	Underweight (lb.)	Symptoms	Signs			Radioscopy		Electrocardiogram	Associated lesions	Progress
					B.P.	1st heart sound	2nd aortic sound	Cardiac enlargement	Prominence of right ventricle			
1	M 6/52	Birth	—	LVF at 5/52	—	N	N	− (birth) +++ (5/52)	−	LVH	—	P.M. 6/52
2	M 12	3	11	−	90/60	Spl.	A	−	−	N	A.I.	—
3	M 24	3	21	+	120/90	Spl.	N	−	+	LVH	—	—
4	M 15	8	28	++	96/76	N	N	−	++	LVS	—	Death 15 yrs.
5	F 15	10/12	14	++	80/70	Spl.	N**	+	++	LVS	—	Op. 14 yrs.
6	M 18	3	14	−	120/80	Spl.	N	−	−	LVS	A.I.	—
7	M 7	4½	—	−	90/60	Spl.	N	−	−	N	—	—
8	F 6	1	—	−	110/70	N	N	−	−	N	—	—
9	M 2	1/12	—	−	110/80	Spl.	N	−	−	N	—	—
10	M 14	13*	—	+	160/114	Spl.	A	+	−	LVH	Coarct.†	Resection of coarctation
11	M 25	9	22	++	120/80	Spl.	N**	−	+	LVS	—	Op. 24 yrs.
12	M 15	5	—	—	120/80	Spl.	D**	−	−	LVS	—	Op. 14 yrs.
13	M 8	1	—	—	100/54	Spl.	N	−	+	LVH	A.I.	—
14	M 10/52	7/52	—	LVF at 7/52	160/90	N	N	+	−	LVS	Coarct.	P.M. 10/52
15	M 9	5	—	−	80/60	Spl.	N	−	−	N	—	—
16	M 14	5	14	+	100/80	Spl.	A	−	−	N	—	Op. 13 yrs.
17	M 11	5/12	21	+	110/90	N	D**	++	+	LVS	Coarct.	P.M. 11 yrs.‡
18	M 14	5	7	+	105/28	Spl.	A	−	+	N	A.I.	—
19	M 5	9/12	—	−	110/70	Spl.	N	−	+	N	—	—
20	M 3	3/12	—	−	92/64	N	N	−	−	N	—	—
21	M 9	Birth	—	−	100/80	Spl.	D	−	−	N	—	—
22	M 16	1	14	+	130/70	N	D	−	−	LVS	A.I.	Op. 16 yrs.
23	M 9	4	14	+	100/70	N	N**	−	−	LVS	—	Death 9 yrs.
24	F 8	5	—	−	110/60	N	D	−	−	N	—	—
25	F 20	7	—	−	120/80	N	D	++	−	LVS	—	Op. 19 yrs.
26	F 11	2	7	−	110/80	N	N	−	−	LVS	—	—
27	M 23	4	—	++	130/60	N	N	++	−	LVS	A.I.†	—
28	M 16	1	—	+	120/84	Spl.	N	−	−	N	—	—

Note.—A systolic thrill in the neck or aortic area accompanied the basal systolic murmur in all patients except the two infants (Cases 1 and 14). All details are the most recent available (before death or operation, when applicable).

* Subaortic site of stenosis suggested on angiocardiography. † The predominant lesion. ‡ This boy died from ventricular fibrillation while recovering from anæsthesia after retrograde aortography. ** These patients had an apical mid-diastolic (Reid) murmur.

+: present ++: moderate. +++: severe.

LVF: left ventricular failure. Spl.: split. N: normal. D: diminished. A: accentuated. LVH: left ventricular hypertrophy without inverted T waves. LVS: left ventricular hypertrophy with inverted T waves. A.I.: aortic incompetence. Op.: aortic valvotomy. P.M.: post-mortem examination. Coarct.: coarctation of aorta.

As the years advance the development of a faint blowing aortic diastolic murmur is not uncommon and is probably secondary to increasing rigidity of the deformed valve cusps. Taussig (1947) has emphasized how this evolution contrasts with that in rheumatic aortic stenosis in which the primary lesion is usually incompetence. In the congenital malformation there are seldom peripheral signs of the valvular incompetence but their presence does not exclude a congenital origin. Congenital aortic incompetence is well recognized in coarctation of the aorta, and one of us has seen on routine examination a boy of three years with very free aortic incompetence who had no disability and no history of previous illness, rheumatic or otherwise.

The electrocardiogram is usually normal but may show left ventricular hypertrophy. Radioscopy confirms the absence of cardiac enlargement. Prominence of the ascending aorta is common, but may not be obvious in the younger age group. By the time school years are reached, enlargement of the left ventricle is usually apparent under the X-ray screen in the left anterior oblique position.

The well-being and lack of symptoms in most cases of isolated aortic stenosis, whether encountered in childhood or in adult life and whether the stenosis is mild or severe, has led to the widespread impression that the prognosis in the congenital lesion is good (Grisham *et al.*, 1947; Kiloh, 1950; Campbell and Kauntze, 1953). This is not always so. Congenital aortic stenosis sometimes leads to death in childhood and the particular liability of this lesion to cause sudden death is well recognized (Brown, 1950). The course in the 28 patients in the present series demonstrates that the outlook in congenital aortic stenosis can be serious. The prognosis in mild cases is altogether different from that in severe cases and, as in pulmonary stenosis (Abrahams and Wood, 1951), distinction between the two groups is all-important.

Assessment of Severity

Circulatory Considerations. Assessment of the severity depends on understanding the way in which severe aortic stenosis affects the circulation. A rise of left ventricular pressure and the left ventricular hypertrophy that soon follows combine to maintain cardiac compensation in spite of the obstruction at the aortic orifice. When compensation is complete, the cardiac output is not decreased, arterial pressures are within normal limits, and venous and pulmonary congestion are absent. The heart rate is generally slow and on radioscopy the ventricular action is seen to have a deliberate and purposeful character. Much less stenosis than is necessary to affect the systolic discharge from the left ventricle is sufficient to produce a loud systolic murmur. If the stenosis is severe, and the left ventricular hypertension does not overcome the stenosis, the pressure rises in the left atrium and in the pulmonary circuit. This elevated pressure necessitates a rise of right ventricular pressure which may in turn lead to right ventricular hypertrophy. These circulatory changes have been clearly demonstrated in experimental animals (Wiggers, 1949) and are evident clinically, angiocardiographically, and on cardiac catheterization in man. Direct measurement of the left ventricular pressure at operation (Campbell and Kauntze, 1953) has revealed pressures as high as 216/36 mm. Hg. The effects of these pressures on the heart muscle are evident post mortem in enormous hypertrophy of the left ventricle and significant hypertrophy of the right ventricle.

The circulatory changes emphasize three major factors in the assessment of the severity of the aortic obstruction.

(*a*) By increased force of contraction, compensation is maintained and symptoms are minimal. The presence of symptoms suggests that the stenosis is severe and compensation inadequate.

(*b*) Hypertrophy alone seldom leads to sufficient cardiac enlargement for clinical or radiological detection. Clinical enlargement of the heart is usually due to dilatation, and its presence when there is no associated aortic incompetence suggests that hypertrophy alone has proved inadequate and that the stenosis must be severe.

(*c*) There is no evidence that a congenitally stenosed orifice gets larger with the increasing demands of a growing child. With an orifice of fixed size, compensation that is adequate in early

coarctation of aorta.

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Case No.	Sex and age	Age of recognition (years)	Under-weight (lb.)	Symptoms	Signs			Radioscopy		Electro-cardio-gram	Associated lesions	Progress
					B.P.	1st heart sound	2nd aortic sound	Cardiac enlarge-ment	Prominence of right ventricle			
1	M 6/52	Birth	—	LVF at 5/52	—	N	N	− (birth) +++ (5/52)	−	LVH	—	P.M. 6/52
2	M 12	3	11	−	90/60	Spl.	A	−	−	N	A.I.	—
3	M 24	3	21	+	120/90	Spl.	N	−	+	LVH	—	—
4	M 15	8	28	++	96/76	N	N	−	++	LVS	—	Death 15 yrs.
5	F 15	10/12	14	++	80/70	Spl.	N**	+	++	LVS	—	Op. 14 yrs.
6	M 18	3	14	−	120/80	Spl.	N	−	−	LVS	A.I.	—
7	M 7	4½	—	−	90/60	Spl.	N	−	−	N	—	—
8	F 6	1	—	−	110/70	N	N	−	−	N	—	—
9	M 2	1/12	—	−	110/80	Spl.	N	−	−	N	—	—
10	M 14	13*	—	+	160/114	Spl.	A	+	−	LVH	Coarct.†	Resection of coarctation
11	M 25	9	22	++	120/80	Spl.	N**	−	+	LVS	—	Op. 24 yrs.
12	M 15	5	—	—	120/80	Spl.	D**	−	−	LVS	—	Op. 14 yrs.
13	M 8	1	—	—	100/54	Spl.	N	−	+	LVH	A.I.	—
14	M 10/52	7/52	—	LVF at 7/52	160/90	N	N	+	−	LVS	Coarct.	P.M. 10/52
15	M 9	5	—	−	80/60	Spl.	N	−	−	N	—	—
16	M 14	5	14	+	100/80	Spl.	A	−	−	N	—	Op. 13 yrs.
17	M 11	5/12	21	+	110/90	N	D**	++	+	LVS	Coarct.	P.M. 11 yrs.‡
18	M 14	5	7	+	105/28	Spl.	A	−	+	N	A.I.	—
19	M 5	9/12	—	−	110/70	Spl.	N	−	+	N	—	—
20	M 3	3/12	—	−	92/64	N	N	−	−	N	—	—
21	M 9	Birth	—	−	100/80	Spl.	D	−	−	N	—	—
22	M 16	1	14	+	130/70	N	D	−	−	LVS	A.I.	Op. 16 yrs.
23	M 9	4	14	+	100/70	N	N**	−	−	LVS	—	Death 9 yrs.
24	F 8	5	—	−	110/60	N	D	−	−	N	—	—
25	F 20	7	—	−	120/80	N	D	++	−	LVS	—	Op. 19 yrs.
26	F 11	2	7	−	110/80	N	N	−	−	LVS	—	—
27	M 23	4	—	++	130/60	N	N	++	−	LVS	A.I.†	—
28	M 16	1	—	+	120/84	Spl.	N	−	−	N	—	—

Note.—A systolic thrill in the neck or aortic area accompanied the basal systolic murmur in all patients except the two infants (Cases 1 and 14). All details are the most recent available (before death or operation, when applicable).

* Subaortic site of stenosis suggested on angiocardiography. † The predominant lesion. ‡ This boy died from ventricular fibrillation while recovering from anæsthesia after retrograde aortography. ** These patients had an apical mid-diastolic (Reid) murmur.

+: present ++: moderate. +++: severe.

LVF: left ventricular failure. Spl.: split. N: normal. D: diminished. A: accentuated. LVH: left ventricular hypertrophy without inverted T waves. LVS: left ventricular hypertrophy with inverted T waves. A.I.: aortic incompetence. Op.: aortic valvotomy. P.M.: post-mortem examination. Coarct.: coarctation of aorta.

As the years advance the development of a faint blowing aortic diastolic murmur is not uncommon and is probably secondary to increasing rigidity of the deformed valve cusps. Taussig (1947) has emphasized how this evolution contrasts with that in rheumatic aortic stenosis in which the primary lesion is usually incompetence. In the congenital malformation there are seldom peripheral signs of the valvular incompetence but their presence does not exclude a congenital origin. Congenital aortic incompetence is well recognized in coarctation of the aorta, and one of us has seen on routine examination a boy of three years with very free aortic incompetence who had no disability and no history of previous illness, rheumatic or otherwise.

The electrocardiogram is usually normal but may show left ventricular hypertrophy. Radioscopy confirms the absence of cardiac enlargement. Prominence of the ascending aorta is common, but may not be obvious in the younger age group. By the time school years are reached, enlargement of the left ventricle is usually apparent under the X-ray screen in the left anterior oblique position.

The well-being and lack of symptoms in most cases of isolated aortic stenosis, whether encountered in childhood or in adult life and whether the stenosis is mild or severe, has led to the widespread impression that the prognosis in the congenital lesion is good (Grisham *et al.*, 1947; Kiloh, 1950; Campbell and Kauntze, 1953). This is not always so. Congenital aortic stenosis sometimes leads to death in childhood and the particular liability of this lesion to cause sudden death is well recognized (Brown, 1950). The course in the 28 patients in the present series demonstrates that the outlook in congenital aortic stenosis can be serious. The prognosis in mild cases is altogether different from that in severe cases and, as in pulmonary stenosis (Abrahams and Wood, 1951), distinction between the two groups is all-important.

Assessment of Severity

Circulatory Considerations. Assessment of the severity depends on understanding the way in which severe aortic stenosis affects the circulation. A rise of left ventricular pressure and the left ventricular hypertrophy that soon follows combine to maintain cardiac compensation in spite of the obstruction at the aortic orifice. When compensation is complete, the cardiac output is not decreased, arterial pressures are within normal limits, and venous and pulmonary congestion are absent. The heart rate is generally slow and on radioscopy the ventricular action is seen to have a deliberate and purposeful character. Much less stenosis than is necessary to affect the systolic discharge from the left ventricle is sufficient to produce a loud systolic murmur. If the stenosis is severe, and the left ventricular hypertension does not overcome the stenosis, the pressure rises in the left atrium and in the pulmonary circuit. This elevated pressure necessitates a rise of right ventricular pressure which may in turn lead to right ventricular hypertrophy. These circulatory changes have been clearly demonstrated in experimental animals (Wiggers, 1949) and are evident clinically, angiocardiographically, and on cardiac catheterization in man. Direct measurement of the left ventricular pressure at operation (Campbell and Kauntze, 1953) has revealed pressures as high as 216/36 mm. Hg. The effects of these pressures on the heart muscle are evident post mortem in enormous hypertrophy of the left ventricle and significant hypertrophy of the right ventricle.

The circulatory changes emphasize three major factors in the assessment of the severity of the aortic obstruction.

(*a*) By increased force of contraction, compensation is maintained and symptoms are minimal. The presence of symptoms suggests that the stenosis is severe and compensation inadequate.

(*b*) Hypertrophy alone seldom leads to sufficient cardiac enlargement for clinical or radiological detection. Clinical enlargement of the heart is usually due to dilatation, and its presence when there is no associated aortic incompetence suggests that hypertrophy alone has proved inadequate and that the stenosis must be severe.

(*c*) There is no evidence that a congenitally stenosed orifice gets larger with the increasing demands of a growing child. With an orifice of fixed size, compensation that is adequate in early

coarctation of aorta.
hypertrophy with inverted T waves. A.I.: aortic incompetence. Op.: aortic valvotomy. P.M.: post-mortem examination. Coarct.:

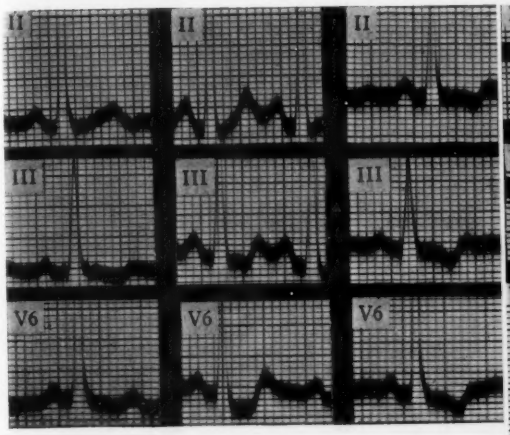
childhood may become inadequate as body growth proceeds. Stenosis that appears mild in early childhood may prove severe before adult life is reached.

Symptoms. The onset of symptoms, as in isolated pulmonary stenosis, is late in the natural history of aortic stenosis. " The immunity from suffering is due to the great increase of power in the heart, and especially the left ventricle, so as to enable it to maintain the circulation " (Peacock, 1868). Even slight disability is significant. The commonest complaint is a tendency to fatigue by the end of the day. Exertional dyspnœa is seldom sufficient to attract attention and its absence does not exclude severe stenosis. Lewes (1951) has stressed the severe prognostic significance of symptoms in aortic stenosis and Marvin and Sullivan (1935) have suggested that cardiac syncope is a precursor of sudden death. Cardiac syncope is always ominous although not necessarily incompatible with several years of life even in growing children. In Case 23 there were three minor episodes of syncope on exertion between 3 years and the attack in which death occurred at 9 years. In Case 4 dizziness on severe exertion had been present for a year and the first major episode of syncope occurred five months before sudden death at 15 years of age. In older patients with aortic stenosis, angina of effort is common and may be secondary to severe stenosis or to advanced coronary atherosclerosis in association with mild stenosis (Dry and Willius, 1939; Anderson *et al.*, 1952). Angina was present in only one of the present series (Case 3). In him it was mild, and considerable exertion was required to produce a momentary sensation of substernal constriction. A vigorous exercise test, however, produced striking ST–T wave changes (Fig. 1). Similar changes occurred in Case 16 without the production of pain. The frequency of this type of cardiographic change in aortic stenosis and its prognostic value are not yet known. Lewes (1951) found angina an indication of severe stenosis and that patients subject to it were liable to sudden death. Hæmoptysis is a rare presenting symptom in aortic stenosis, but occurred in one patient in the present series (Case 11) who had other indications of very severe stenosis. It has been observed also in a patient with severe coarctation of the aorta whose pulmonary arterial pressure on cardiac catheterization ranged from 35–50/15 mm. Hg. Like ischæmic pain hæmoptysis suggests severe stenosis but is too uncommon in the younger age group for a firm conclusion on its prognostic significance.

Signs. As a general rule, signs appear earlier and are of much greater value than symptoms in the assessment of the severity of aortic stenosis. Only by the recognition of this fact can sudden death be anticipated and prevented by timely surgery. In general appearance the patient with severe aortic stenosis tends to be pale, thin, and poorly developed and may be as much as 28 lb. under average weight in the early teens (Case 4). Twelve of the present series were more than 7 lb. under the standard weight for their age. It is unusual for the patient with severe congenital aortic stenosis to be of heavy muscular build, but there are exceptions (Case 12). Brown (1950) mentions pallor and small stature as common features in aortic stenosis, but states that these characteristics may be lacking when the stenosis is mild. The build of the patient bears a much closer relationship to the severity of the lesion than it does in coarctation of the aorta.

The pulse and blood pressure are unreliable signs in the diagnosis of aortic stenosis (Kiloh, 1950; Lewes, 1951) but are of undoubted value in the recognition of the severity of the malformation. The smallness of the pulse pressure depends upon the degree of the stenosis, although the pulse pressure is often larger than might be expected (Wiggers, 1949). A normal pulse pressure on sphygmomanometry does not exclude severe stenosis, but a delay in the upstoke of the pulse wave revealed on intra-arterial pressure tracings (Fig. 3) is probably a reliable guide to the severity of the stenosis. A true anacrotic notch is a rare clinical finding. Wiggers (1949) has shown experimentally that the aortic orifice has to be reduced to one-quarter of its normal size before the form of the arterial pulse wave is affected, and that the more severe the stenosis, the lower the anacrotic notch occurs on the upstroke. These observations emphasize the significance of the form of the intra-arterial wave in this malformation.

The type of præcordial pulsation and the character of the apical impulse are of little assistance in



A B C

FIG. 1.—Electrocardiogram of Case 3 at 24 years of age. (A) At rest. (B) Immediately after strenuous exercise—17,280 ft. lb. in three minutes—S–T depression in V6. (C) Five minutes after exercise—inversion of the T wave in leads II, III, and V6.

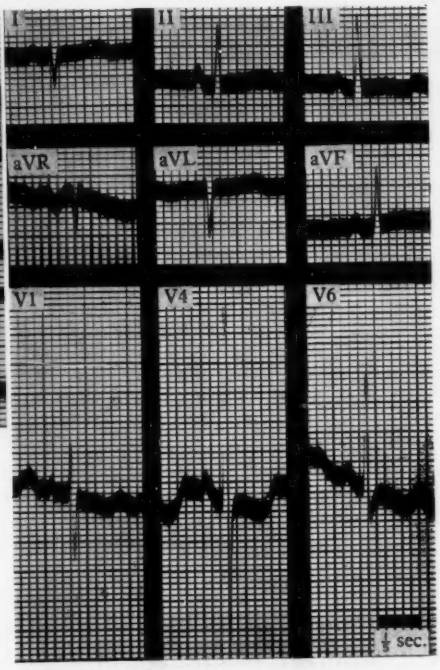
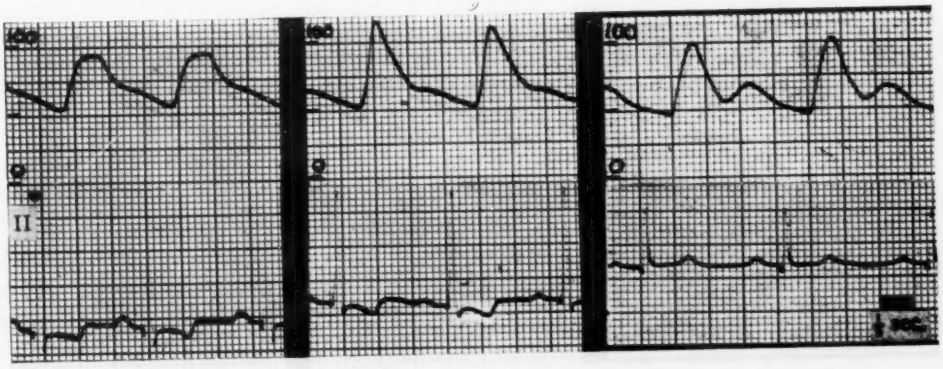


FIG. 2.—Electrocardiogram of Case 1 at three days of age. Right axis deviation. Early evidence of left ventricular hypertrophy in V4 and V6 in which leads R waves are tall and T waves diphasic.



A B C

FIG. 3.—Intra-arterial brachial pulse wave in Case 11. (A) Before valvotomy; B.P. 95/45, upstroke 0·24 sec. (B) Three weeks after valvotomy; B.P. 110/50, upstroke 0·10 sec. (C) Normal control; B.P. 100/45, upstroke 0·12 sec.

either the diagnosis or the assessment of aortic stenosis of congenital origin. The forceful, heaving impulse found in the older age groups may be conspicuously absent, even when the cardiogram shows extreme left ventricular hypertrophy. The first heart sound at the apex and lower left sternal margin tends to be loud and widely split, but this feature, like the intensity of the basal systolic murmur and thrill, does not bear a constant relationship to the severity of the stenosis. Nevertheless, the finding of a widespread aortic systolic murmur and thrill in early childhood suggests that as growth proceeds the stenosis will be found to be severe. The aortic second sound tends to be diminished in severe aortic stenosis (Dry and Willius, 1939) but is often of normal intensity (Kiloh, 1950; Lewes, 1951; Levine, 1949; Taussig, 1947; Grishman *et al.*, 1947). Diminution of the aortic second sound has proved uncommon in the younger age group of the present series; indeed it has often been loud in the presence of severe stenosis.

A short, rough mid-diastolic murmur of abrupt quality was heard at the apex or just internal to it in five patients (Cases 5, 11, 12, 17, and 23). In none of them was there other clinical evidence of mitral stenosis and in Case 17 the mitral valve was normal post mortem except for marked atheroma (impingement plaque) on the ventricular surface of the medial cusp. In each of these patients there was cardiographic evidence of extreme left ventricular hypertrophy. This murmur was detected on another occasion in a seven-year-old boy with marked hypertension secondary to severe coarctation of the aorta, who also had extreme left ventricular hypertrophy and a normal mitral valve post mortem. This murmur is presumably dynamic in origin and secondary to gross left ventricular hypertrophy and intraventricular hypertension. It disappeared after aortic valvotomy in Cases 5, 11, and 12. We have heard this apical murmur of severe aortic stenosis referred to as Reid's murmur but have been unable to trace the original reference.

Ancillary Investigations

Electrocardiographic evidence of left ventricular hypertrophy has proved the most reliable single sign of severe aortic stenosis. The development of left ventricular hypertrophy closely parallels the development of right ventricular hypertrophy in pulmonary stenosis (Marquis, 1951). The earlier in childhood that this appears and the more rapid its progression, the more severe the stenosis and the worse the prognosis. This is impressively demonstrated in those patients of the present series in whom aortic stenosis proved fatal. In Case 1 there was already evidence of left ventricular hypertrophy three days after birth (Fig. 2) and in Case 14 there was deep T wave inversion and S–T depression in the left chest leads at seven weeks of age. In Case 23, left ventricular hypertrophy developed between five and eight years of age (Fig. 4). In Case 17, the hypertrophy was of extreme degree at five years of age, and in Case 4 (Fig. 5) at 11 years of age. No patient died without the development of inverted T waves in the left chest leads except the infant (Case 1), in whom the only cardiogram recorded was at the age of three days. Sixteen out of the whole series showed cardiographic evidence of left ventricular hypertrophy, and in twelve of them there was T wave inversion in leads facing the epicardial surface of the left ventricle. The development of left ventricular hypertrophy in adult life, after growth has ceased and the cardiac output is no longer increasing with age, is probably of less immediate prognostic significance, but is an indication for full investigation. Abnormal ballistocardiograms, grades 2 and 3 as described by Brown *et al.* (1950), are also frequent in aortic stenosis. Our experience is inadequate for a proper appreciation of their value in assessing severity.

The infrequency of cardiac enlargement on radioscopy has been stressed by Kiloh (1950) and Campbell and Kauntze (1953). In contrast to the cardiographic pattern, there is little or no increase in heart size or in the size of the left ventricle with the passage of years. This general rule obtains even in the presence of severe stenosis; there was no increase in the size of the heart during the last year of life in Cases 4 and 23. In the absence of significant aortic incompetence, marked enlargement is due to ventricular failure (Fig. 6) or to a quite exceptional degree of hypertrophy. It is always indicative of very severe stenosis and of very poor immediate prognosis. The shape of the

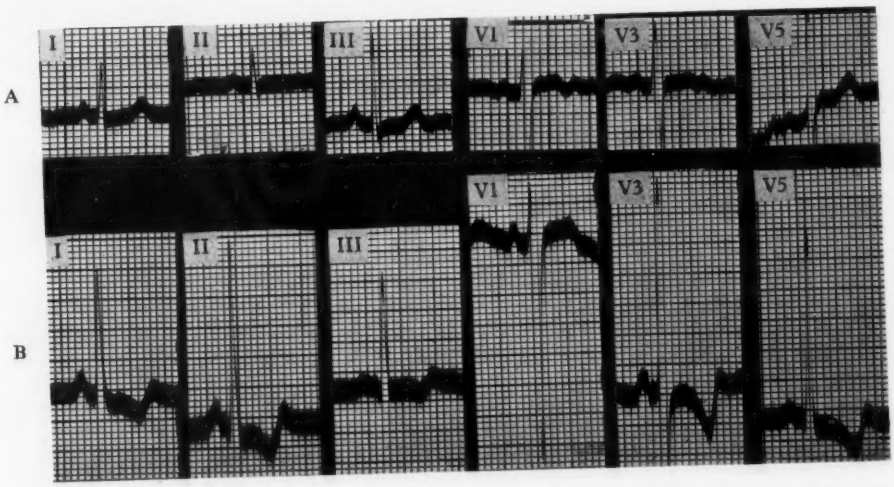


FIG. 4.—Electrocardiogram of Case 23. (A) Within normal limits at 5 years of age. (B) Left ventricular hypertrophy and strain at eight years of age.

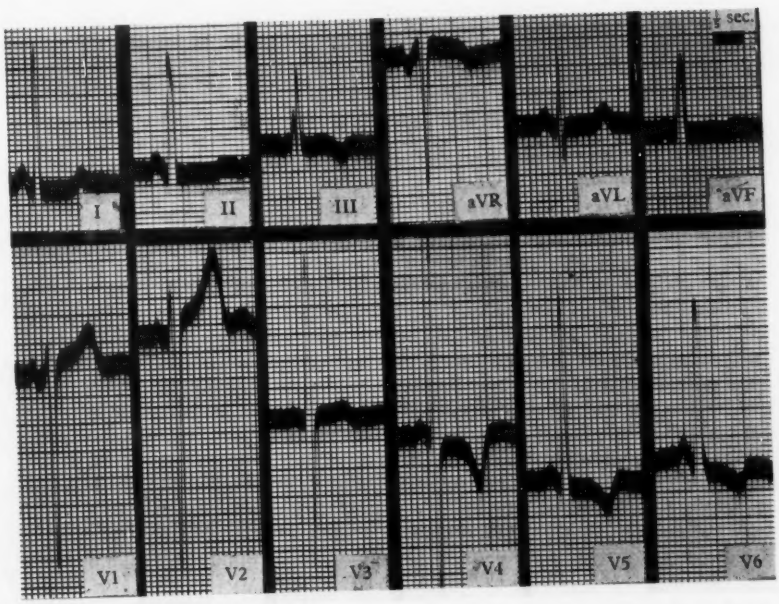
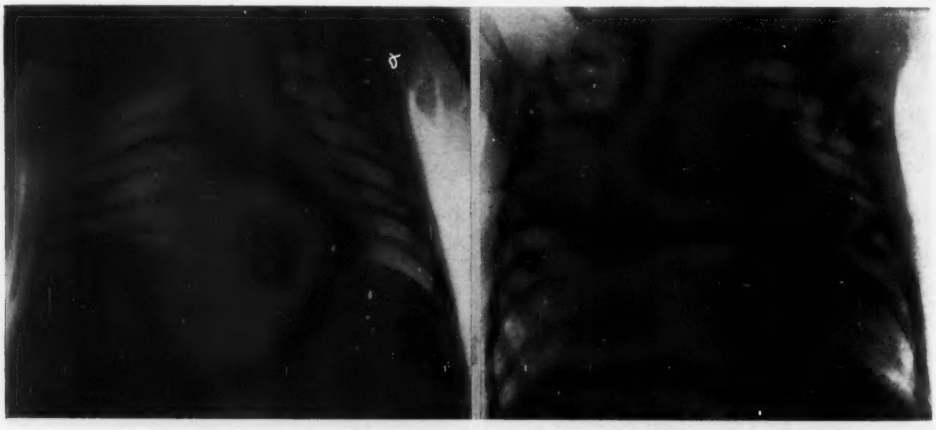


FIG. 5.—Electrocardiogram of Case 4 shortly before his sudden death at 15 years of age. No axis deviation. Extreme left ventricular hypertrophy and strain.

cardiovascular shadow may also be of help in assessing the severity of the stenosis, and the strain it is imposing upon the circulation, by revealing prominence of the right ventricle in the left anterior oblique position (Fig. 7). This was well seen in eight cases, the presence of right ventricular hypertrophy being confimed post mortem in Case 16. Right ventricular hypertrophy in aortic stenosis was noted at autopsy by Peacock (1868), de Veer (1938), and Campbell and Kauntze (1953). Prominence of the right ventricle on radioscopy is less common in older patients with aortic stenosis, possibly because embarrassment of the right ventricle (Bernheim, 1910) leads to failure and death before the pressure in the pulmonary circuit rises. Calcification of the aortic valve was not seen on radioscopy in any of the patients in the present series. This was probably due to their youth (Campbell and Kauntze, 1953) for calcification bears little relation to the severity of the stenosis (Dry and Willius, 1939).



A B

FIG. 6.—Radiograph (anterior) of Case 1. (A) At three days of age. Heart size within normal limits. (B) At five weeks of age. Gross enlargement of the heart with central congestion of the lung fields.

Angiocardiographic examination was performed in 10 of the series as part of their assessment for surgical treatment. This investigation was undertaken in an attempt to exclude subaortic stenosis. In only one was subaortic stenosis (Fig. 9) suggested, and in the remainder the contrast medium was clearly seen filling the left ventricle up to the origin of the aorta without apparent narrowing of the outflow tract; the lateral position was found of most value is displaying this (Fig. 8). Although no evidence of subaortic obstruction was encountered at operation in the six patients upon whom subsequent valvotomy was performed, we cannot be certain that this appearance excludes its presence. The angiocardiograms suggested delayed clearing of the left side of the heart in five patients (Cases 3, 11, 12, 17, and 22) in so far as the left ventricle was not clear of contrast medium within six seconds of first opacification. In only one (Case 5) was there indisputable hold-up throughout the circulation (Fig. 8 and 10). This is a visual demonstration of cardiac insufficiency, and illustrates clearly the effect that aortic stenosis can have on the circulation: it constitutes certain evidence of severe stenosis. Cardiac catheterization has not been performed as a routine in the investigation of these patients before operation but the small pulmonary arteries in Case 17 showed similar changes post mortem to those seen in pulmonary hypertension secondary to mitral stenosis. A raised pulmonary arterial pressure was present in two of the cases reported by Campbell and Kauntze (1953) and as a manifestation of left ventricular insufficiency this is probably another sign of severe aortic stenosis.

FIG. 7.—Radiograph (left anterior oblique) of Case 4 at 15 years of age, showing prominence of the right as well as of the left ventricle.

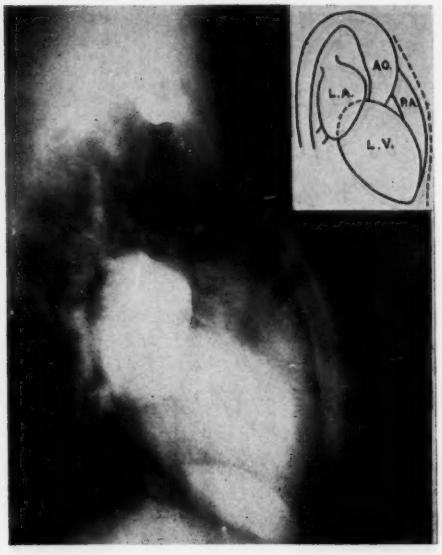


FIG. 8.—Angiocardiogram (lateral) at 13 seconds of Case 5 before valvotomy. The concentration of the dye in the left ventricle up to the origin of the aorta probably excludes subaortic obstruction. The delayed circulation is well illustrated by the concentration of dye on the left side of the heart, the poor opacification of the aorta and by the persistence of dye in the pulmonary artery.

SURGICAL CONSIDERATIONS

If the stenosis is severe, valvotomy may possibly improve the prognosis. The assessment for surgical treatment and the timing of operation require an understanding of the anatomy of the stenosis and its effect upon the myocardium, and also practical experience of operative treatment and the results that may be achieved by aortic valvotomy.

Anatomy of Aortic Stenosis. The anatomy of the stenosis varies according to its ætiology. There are some grounds for expecting cusps fused by rheumatism to separate along the commissures without the production of aortic incompetence (Larzelere and Bailey, 1953; Logan and Turner, 1954). Good post-operative function of the cusps is unlikely in the congenital lesion. In the present series an attempt has been made to consider congenital stenosis only, but it is important to realize that there is no combination of clinical signs that makes this ætiological diagnosis certain. Pathological evidence likewise is seldom valid. The finding of bicuspid valves at necropsy does not imply that any stenosis present is necessarily of congenital origin, for there is no reason to expect acquired stenosis to be confined to valves with three cusps. Indeed, Peacock (1865) considered that congenitally deformed valves have an increased tendency to become diseased.

The distinction between valvular and subaortic stenosis is also difficult. Both types are liable to considerable post-stenotic dilatation of the ascending aorta and the location of the maximum murmur and thrill is unreliable evidence of the site of stenosis. Angiocardiography (Fig. 9) will probably prove of assistance, but there is insufficient evidence to be sure of this. The problem, however, is largely theoretical for subaortic stenosis as an isolated lesion appears to be very uncommon and rarely of sufficient severity to require operative treatment.

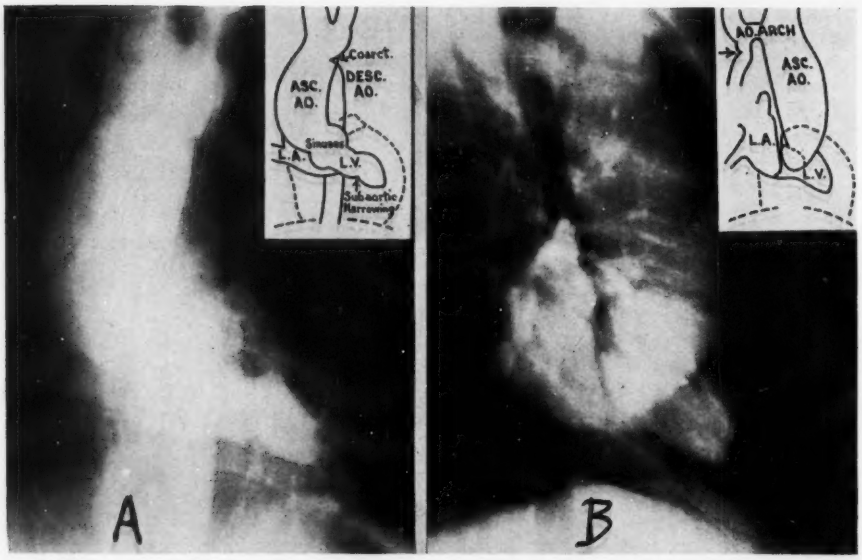


FIG. 9.—Angiocardiograms at 8 seconds of Case 10 at 12 years of age. (A) Anterior. Serial films showed persistence of the area of constriction in the left ventricle during both systole and diastole. (B) Lateral. This view emphasizes the low position of the aortic valve and the dilatation of the ascending aorta also evident in the anterior view. The angiocardiographic appearances suggest mild subaortic stenosis. At operation for the coarctation of the aorta, inspection of the left ventricle revealed no external deformity but a systolic thrill was felt below as well as above the aortic valve.

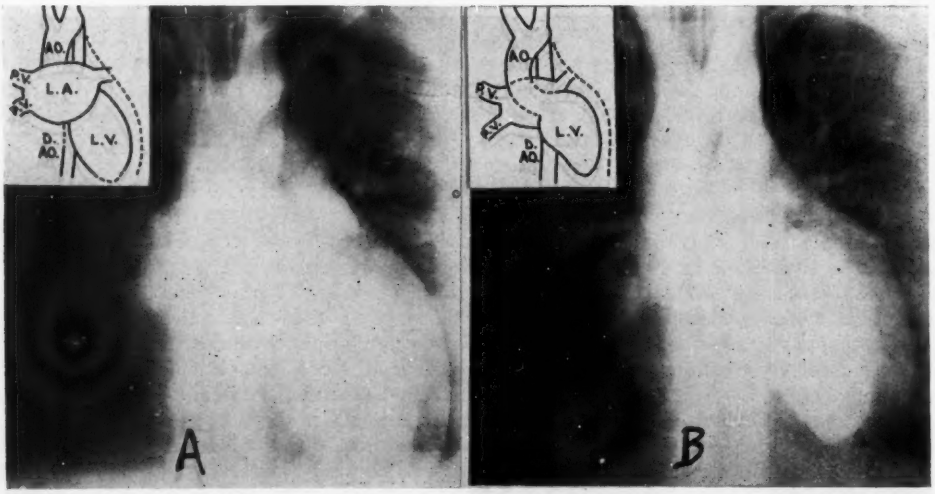


FIG. 10.—Angiocardiograms (anterior) of Case 5. (A) Before valvotomy. At 13 seconds the aorta is still poorly opacified and much less dense than the large left atrium (which dominates the picture) and thick-walled left ventricle. (B) Three weeks after valvotomy. At 7 seconds the aorta is already as dense as the left ventricle. The cavities of the left atrium and left ventricle are smaller than before operation.

Necropsy findings were available in three patients of the present series, in all of whom the stenosis was severe. In one infant of 10 weeks (Case 14) there were three cusps which were narrow and adherent at their free margins making a cone similar to that of congenital pulmonary stenosis: there was no thickening of the cusps except at their free margins. In the other two patients, an infant of six weeks (Case 1) and a boy of 11 years (Case 17), there were two cusps which were thick, opaque, hard, and fibrosed. The great deformity of this type of valve, illustrated in Fig. 11, is not uncommon in congenital aortic stenosis. The fact that bicuspid valve cusps may be so deformed in infancy (Case 1) suggests that the gross deformity common in older patients is not only the result of long continued trauma. Nevertheless, the traumatic effect of high pressure cannot be ignored; the occurrence of degenerative aortic stenosis emphasizes its importance. The later development of stenosis in rheumatic aortic incompetence and the impression that bicuspid aortic valves are particularly liable to develop stenosis suggest that aortic cusps that are already damaged tend to become stenosed. Some recurrence of the stenosis after valvotomy, therefore, appears probable.

FIG. 11.—Aortic valve in Case 17 who died at 11 years of age. The valve is bicuspid and shows gross deformity, thickening, and fibrosis.

Effect of Aortic Stenosis on Myocardium. The extent and nature of fibrosis of the left ventricle (Fig. 12) found post mortem in an 11-year-old boy (Case 17) is an impressive illustration of the effect of severe aortic stenosis on the myocardium. The fibrosis is a replacement lesion secondary to death of the muscle cells which on examination under high power can be seen distintegrating in the subendocardial half of the myocardium. It is thus quite distinct from the fibrosis seen in chronic myocardial hypertrophy (Harrison and Wood, 1949) and bears a closer relationship to the " zonal ring infarction " described by Fulton (1954). The frequency of such severe myocardial fibrosis in aortic stenosis is not known. The same zonal subendocardial distribution has been seen in a man 49 years old in whom aortic stenosis had been diagnosed first on routine examination at 18 years of age, and in whom the coronary vessels were unusually large and healthy. In both these patients the myocardial fibrosis was confined to the left ventricle although in one of them (Case 17) there was also hypertrophy of the right ventricle. This localization of the fibrosis to the left ventricle is the counterpart of the fibrosis of the right ventricle in pulmonary stenosis (Allenby and Campbell, 1949). It emphasizes the importance of outlet stenosis in the causation of the fibrosis.

The occurrence of anginal pain in both forms of stenosis, their common liability to cause sudden death, the necrobiosis of the muscle cells, the subendocardial distribution of the fibrosis and the electrocardiographic changes on exercise (Fig. 1) combine to suggest that the fibrosis may be secon-

dary to ischæmic destruction of the muscle cells. There is much experimental work to support this suggestion (Green, 1936; Johnson and di Palma, 1939; Wiggers, 1949), but in the absence of accurate assessment of the phasic coronary blood flow through the intra-mural vessels (Gregg, 1946), the evidence is not conclusive.

Aortic Valvotomy. Bailey has pioneered the transventricular approach to the aortic valve, and has shown division of the commissures to be a feasible procedure in aortic stenosis of rheumatic origin (Larzelere and Bailey, 1953). If good results are to be obtained in congenital stenosis, operation should anticipate the development of myocardial fibrosis and calcification of the valve. In theory, therefore, valvotomy should be performed as soon as the severity of the stenosis is certain. In practice, the position is complicated by the risks of the procedure.

The value of operation and the extent of its application can be determined only by experience. A short pilot study was therefore planned. Six patients (Cases 5, 11, 12, 16, 22, and 25), in whom the clinical picture suggested in different ways a severe degree of aortic stenosis, were selected for operation. In each case the approach was through the left ventricular wall, and an expanding dilator introduced into the aortic orifice was opened to its full extent (4 cm.) in two or more directions without prior incision of the valve. It was thought probable that division in the best line of cleavage was as likely to be achieved in this way as by the more elaborate technique now advocated in acquired stenosis (Bailey *et al.*, 1954).

Case 5. Female, 14 years. Slight dyspnœa and fatigue since five years. Episode of ankle swelling and cardiac syncope three months before operation.

Tearing sensation as dilator opened in aortic orifice. Immediate decrease in heart size. Uneventful post-operative course. Angiocardiography showed correction of delayed circulation (Fig. 8 and 10). Faint aortic diastolic murmur first detected three months after operation. Symptom-free six months after operation.

Case 11. Male, 24 years. Slight dyspnœa since 14 and worse since 22 years. Extreme left ventricular hypertrophy in first cardiogram at 20 years.

No sensation of tearing as dilator opened. Slight post-operative aortic incompetence with increase in heart size. Ballistocardiographic regression from grade 3 to grade 1 abnormality. Less dyspnœic but not symptom-free six months after operation.

Case 12. Male, 14 years. No disability but cardiographic evidence of marked left ventricular hypertrophy.

Sensation of tearing as dilator opened. Slight post-operative aortic incompetence with increase in heart size. Ballistocardiographic regression from grade 3 to grade 1 abnormality (Fig. 13). Increased energy six months after operation in spite of progression of aortic incompetence.

Case 16. Male, 13 years. Easily tired since five years. No cardiographic evidence of left ventricular hypertrophy but ischæmic changes on exertion and grade 3 abnormality of ballistocardiogram.

Sensation of calcification at aortic valve with tearing as dilator opened. Diastolic thrill of aortic incompetence immediately after valvotomy. Post-operative course complicated by gross cardiac enlargement and portal and pulmonary congestion. Less easily tired and more robust six months after operation in spite of free aortic incompetence (Fig. 14).

Case 22. Male, 16 years. Never strong. Slight dyspnœa since 13 years with development of cardiographic evidence of left ventricular hypertrophy between 14 and 16 years.

Tearing sensation as dilator opened with immediate thrill of increased aortic incompetence. Moderate post-operative cardiac enlargement in spite of prophylactic digitalization. Stronger and less dyspnœic six months after operation in spite of free aortic incompetence.

Case 25. Female, 19 years. No disability. Keen sportswoman. Cardiographic evidence of marked left ventricular hypertrophy in first record at 16 years.

No sensation of tearing when dilator opened, but muscular resistance at full expansion. Uneventful post-operative course. Increased energy six months after operation.

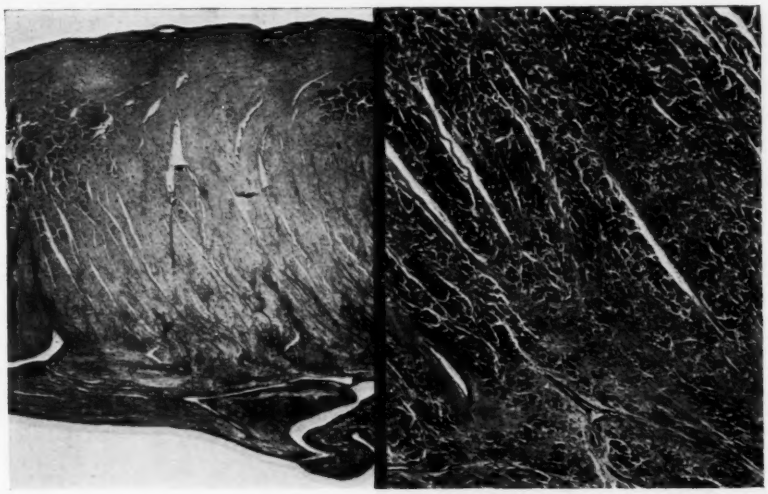


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FIG. 12.—Photomicrograph of myocardium of left ventricle in Case 17 at 11 years of age. (A) full thickness of ventricular wall (×5. Mallory's stain). There is replacement fibrosis which is greatest in the subendocardial zone. (B) The extent of the fibrosis at the junction of middle and subendocardial thirds (×25. Masson's stain).

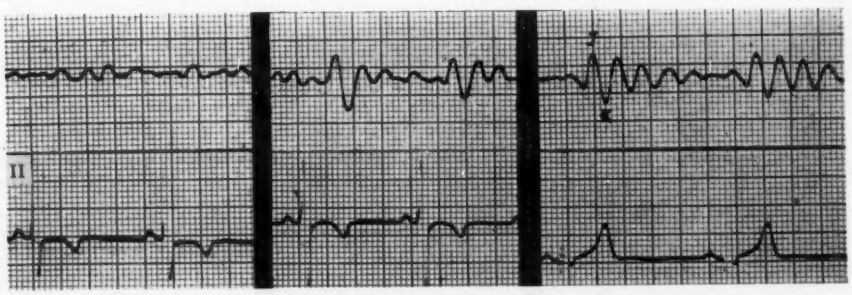

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FIG. 13.—Ballistocardiogram (inspiration with filter in) of Case 12. (A) Before valvotomy: grade 3 abnormality; the complexes remain identifiable but their amplitude is small. (B) Three weeks after valvotomy: grade 1 abnormality; the striking increase in the K wave may be partially due to aortic incompetence produced by operation. (C) Normal control. Ballistocardiograms recorded by the method described by Jacobs (1954).

RESULTS OF SURGERY

The results in the six patients (Table II) in this pilot study have been fairly satisfactory. None died as a result of the operation, three have received undoubted benefit, and there is no certain evidence during over six months' observation that any patient has been made worse.

The reduction in the intensity of the signs of aortic stenosis has been striking in all patients. Where a systolic thrill is still detectable, this has become localized and difficult to feel. Although

TABLE II

RESULTS OF OPERATION—6 PATIENTS—CONGENITAL AORTIC STENOSIS

Case No.	Weight (lb.)		Blood pressure (mm. Hg)		Pulse upstroke (seconds)		Systolic thrill		Systolic murmur grade (Levine)		Signs of aortic incompetence		Cardio-thoracic ratio		Electrocardiogram	
	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.
5	92	108	80/70	130/80	—	—	+++	—	4	3	—	+	52·9 (13·5/25·5)	50·2 (12·4/24·7)	L.V.S.	Flat T waves
11	143	147	120/80	148/64	0·24	0·12	+++	—	5	3	—	++	45·1 (12·5/27·7)	46·2 (13·4/29·0)	L.V.S.	Reduced L.V.S.
12	124	139	120/80	140/54	—	0·12	+++	+	5	4	—	++	49·8 (14·2/28·5)	53·7 (16·1/30·0)	L.V.S.	Flat T waves
16	93	111	100/80	114/50	0·16	0·10	+++	—	5	3	—	+++	44·7 (11·4/25·5)	53·9 (14·4/26·7)	N.A.D.	No change
22	100	111	130/70	140/40	0·20	0·12	+++	+	5	4	+	+++	46·9 (12·1/25·8)	52·7 (13·7/26·0)	L.V.S.	No change
25	136	139	120/80	120/80	0·24	0·12	+++	—	6	3	—	—	52·7 (16·3/30·9)	52·3 (16·1/30·8)	L.V.S.	Flat T waves

Note.—All post-operative records, except those of pulse upstroke, were made six months after operation.

the intensity of the systolic murmur has seldom been reduced by more than one grade, it has become localized to the aortic area. Those who had Reid murmurs have them no longer. Where pulse tracings have been recorded after operation, the upstroke of the wave has returned to normal. In the one patient in whom no such tracing was taken, the blood pressure has increased from 80/70 to 130/80 mm. Hg. These changes are more than is usual after pulmonary valvotomy; it is reasonable to assume that the actual stenosis has been as satisfactorily relieved and that the functional relief has been greater. The disappearance of symptoms in one patient, their partial relief in another, and the sensation of increased well-being in those who had few symptoms before operation suggest that there has been some improvement of cardiac function in them all. Reduced electrocardiographic evidence of left ventricular strain (Fig. 15), ballistocardiographic improvement (Fig. 13), reduction of heart size with disappearance of the delayed circulation on angiocardiography in one patient (Fig. 10), and an average weight increase of 11 lb. during the first six months after operation add support to the suggestion of improved cardiac function.

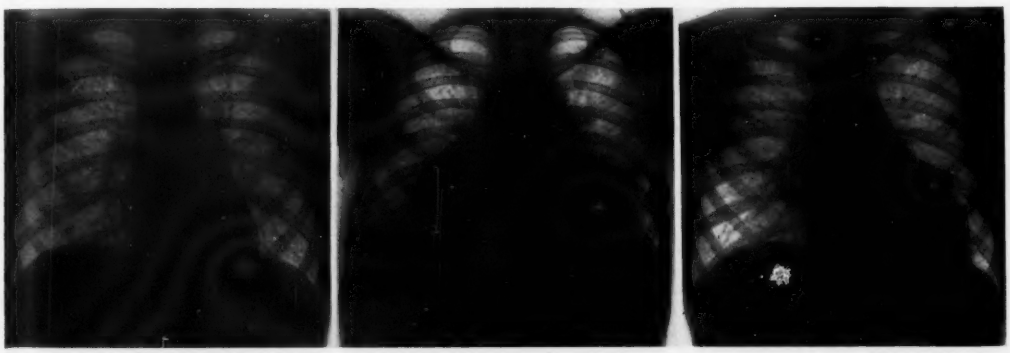

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FIG. 14.—Radiograph (anterior) of Case 16. (A) Before valvotomy showing no enlargement (c.t.r. 44·7). (B) Three weeks after valvotomy with gross enlargement suggesting pericardial effusion. Paracentesis produced less than 2 ml. of slightly blood-stained fluid (c.t.r. 72·4). (C) Six months after valvotomy with moderate enlargement (c.t.r. 53·9).

The manifestations of benefit must be weighed against the effects of aortic incompetence which was produced in four patients and increased in a fifth. This high incidence is not fortuitous. Aortic incompetence sometimes occurs in hypertension when necropsy shows no organic deformity of aortic ring or valve cusps (Garvin, 1940), whereas after pulmonary valvotomy the valve is grossly deformed and yet incompetence is rare. The higher pressures on the left side of the heart demand better valve function than is necessary at the pulmonary orifice. The valve in congenital aortic stenosis is initially more deformed and acquires grosser irregularity than in pulmonary stenosis. Even in young patients without calcification of the aortic valve, it would be over-optimistic to expect normal valve function even if the valve were divided under direct vision. This substitution of one disease by another can never be considered satisfactory therapy, especially when the severity of the disease produced is unpredictable. Although there was immediate evidence of aortic incompetence after completion of the valvotomy in two patients, there seems to us no advantage in the partial relief of the stenosis suggested by Bailey *et al.* (1954).

Assessment of the severity of the aortic incompetence produced is a prime consideration in any appreciation of the results of aortic valvotomy. In three patients the auscultatory evidence of

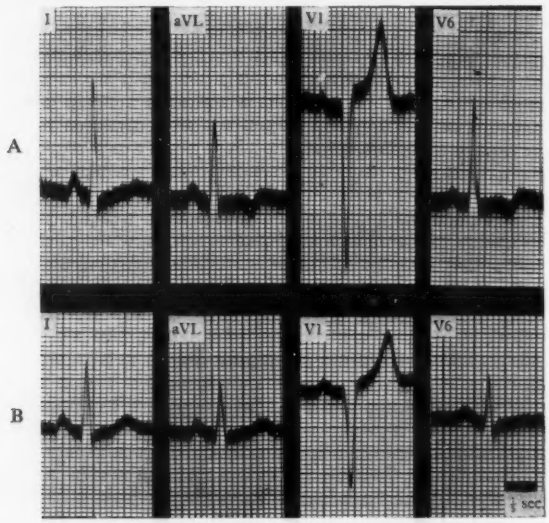

FIG. 15.—Electrocardiogram of Case 25. (A) Before valvotomy, showing left ventricular hypertrophy with T wave inversion in aVL and V6. (B) Six months after valvotomy, showing less left ventricular hypertrophy and T waves upright or flat instead of inverted in aVL and left chest leads (V6).

incompetence is accompanied by a collapsing peripheral pulse. The fact that intra-arterial pulse tracings in these patients show an increase in systolic pressure without a fall in diastolic pressure (Fig. 16) is of interest, but it would be a mistake at this stage to attach much importance to this observation. There was some increase in the heart size soon after the operation in all patients except one (Case 5): this was maximum three weeks after operation, and was sometimes very great (Fig. 14). In every case this enlargement decreased again between three weeks and three months after operation. There was further decrease by the sixth month, except in two patients with severe incompetence (Cases 16 and 22), whose hearts enlarged slightly between the third and sixth months after operation. When pulse pressure, heart size, and auscultatory signs are correlated, the aortic incompetence that followed the operation can be classified as severe in two patients (Case 16 and 22), moderate in two (Cases 11 and 12), and insignificant in one (Case 5).

It is clear that the results of valvotomy in congenital aortic stenosis are not always wholly beneficial and that they are to some extent unpredictable.

ASSESSMENT FOR SURGERY

The indications for valvotomy in congenital aortic stenosis appear much more restricted than they are in pulmonary stenosis and possibly in rheumatic aortic stenosis. The application of a major intra-cardiac operation which carries the additional danger of producing severe aortic incompetence is limited. On the basis of experience in pulmonary valvotomy, it seemed desirable to relieve aortic stenosis as soon as there was sufficient evidence of its severity (Marquis and Gilchrist, 1954). It was on this basis that our six patients were selected for the present pilot study. The possibility of recurrence of the stenosis must also influence the timing of operation. In order to reduce the need for a second operation and for the sake of making as large an orifice as possible,

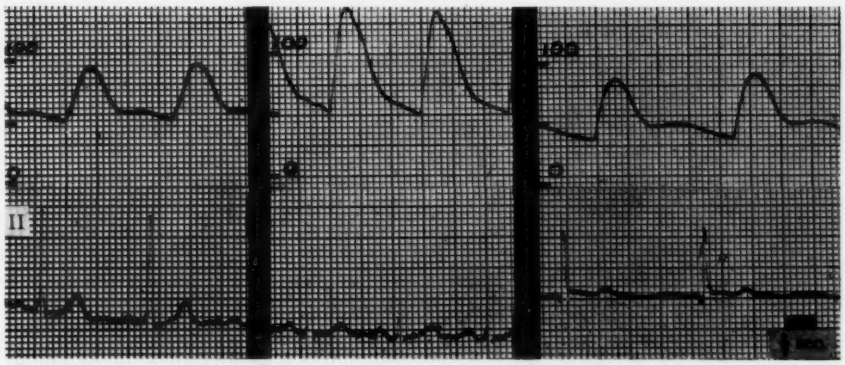

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FIG. 16.—Intra-arterial femoral pulse wave in Case 16. (A) Before valvotomy B.P. 95/50; upstroke 0·16 sec. (B) Three weeks after valvotomy: B.P. 130/50; upstroke 0·12 sec. (C) Normal control: B.P. 90/35; upstroke 0·16 sec.

delay of operation until adult life is desirable if that is compatible with forestalling myocardial fibrosis, valve calcification, and death.

The final decision to operate must be based on the balance between the pre-operative risks of death and irreparable myocardial fibrosis on the one hard, and the risk of the operative procedure itself, and of post-operative aortic incompetence on the other.

The five patients, in whom there is now aortic incompetence, all show some objective evidence of improved cardiac function. Nevertheless in patients similar to Cases 16 and 22, we should now demand more evidence of increasing left ventricular strain, increasing heart size, cardiac syncope, or progressive disability before recommending operation. In patients similar to Case 12, we should want a longer period of observation before deciding on surgery. In contrast, there would be no hesitation in recommending surgery to patients similar to Cases 5, 11, and 25, not because their results are comparatively good, but because their immediate prognosis was bad enough to justify operation in spite of the risk of severe aortic incompetence. Further experience in this type of patient may modify our present policy. It may be that the production of aortic incompetence will prove a lesser risk than progressive myocardial fibrosis. In the meantime, aortic valvotomy is not, in our opinion, justified in congenital stenosis except when there is a danger of sudden death or deterioration of a degree that might prejudice the outcome of postponed surgery. This situation appears to be present when there is electrocardiographic evidence of extreme left ventricular hypertrophy and strain in growing children. The finding of left ventricular strain is important at any age. If it is rapidly progressive, combined with increasing heart size or associated with undoubted hold-up of contrast medium on angiocardiography, it is probably dangerous to delay valvotomy. A history of cardiac syncope or of dizziness or breathlessness on exertion in these circumstaces stresses the urgency of operation.

CONCLUSIONS AND SUMMARY

The course of 28 cases of congenital aortic stenosis is reviewed. The average period of observation was just under four years, during which five patients died.

The lack of symptoms and cardiac enlargement masks the frequency of the more severe grades of congenital aortic stenosis. The prognosis is less good than is widely believed. Once the diagnosis has been made in childhood, annual review is advisable if the warning signs of severity are to be recognized. Electrocardiographic evidence of increasing left ventricular hypertrophy and strain, especially in growing children, is the most reliable indication that the stenosis is severe.

Severe aortic stenosis may lead to extensive fibrosis of the myocardium of the left ventricle, cardiac syncope, or sudden death, without the development of significant exertional dyspnœa.

The aortic stenosis in six of the patients reviewed was considered sufficiently severe to justify their inclusion in a pilot study of aortic valvulotomy. None died as a result of the operation. Their course during the subsequent six months is described. Valvotomy can result in greatly improved cardiac function in congenital aortic stenosis, but is liable to produce severe aortic incompetence. This limits its application to patients in whom the immediate prognosis is poor. In them valvotomy can prove a life-saving operation.

We wish to express our thanks to Dr. A. Rae Gilchrist for his help and encouragement in the preparation of this paper and for permission to report these cases; and to Professor Sir James Learmonth for every facility in the Department of Surgery.

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THE RAUWOLFIA ALKALOIDS IN THE TREATMENT OF HYPERTENSION

BY

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Since the discovery of the hypotensive action of the alkaloids of Rauwolfia serpentina (Chopra, 1933) many reports have appeared dealing with the chemistry, pharmacology, and clinical use of these drugs in hypertension. It is still difficult, however, to give a clear idea as to their exact place in therapy. Many workers have reported extremely good results, with a hypotensive response in one-half to three-quarters of the subjects treated (Hughes *et al.*, 1954; Arnold and Bock, 1953; Hensler, 1953; Vakil, 1953; Chakravarty, 1951) while other reports are more disappointing with a satisfactory response in only 33 per cent (Wilkins and Judson, 1953) and 8 per cent of subjects treated (Löffler, 1953). Nor is it clear from the reports what dosage should be employed. While Freis and Ari (1954) recommend a maintenance dose of 0·2–0·5 mg. reserpine daily others have found this dose completely ineffective and have employed 4·0–6·0 mg. daily of the same substance (Douthwaite, 1954). In a trial designed to clarify these points we were soon impressed by the striking weight increase of most subjects while on rauwolfia and by the appearance of cardiac failure in some. We accordingly modified our procedure to include a study of the influence of this drug on heart output, pulse rate, and fluid balance. The results of these observations are reported below.

Material and Methods

The subjects of this study were 19 ambulatory patients suffering from essential hypertension. Seven were considered to be severe, 6 moderate, and 6 mild in degree (Table I). The type and severity of the condition were assessed by means of clinical examination, retinoscopy, electrocardiography of the heart, examination for chemical and microscopic abnormalities and concentrating power of urine, and an estimate of blood non-protein nitrogen content. Intravenous pyelography was carried out in several cases. Papillœdema was a feature of Cases 4 and 6 only. There was radiological or electrocardiographic evidence of left ventricular hypertrophy in all but two subjects and five complained of some effort dyspnœa. The only evidence of renal impairment was a failure to concentrate urine above a specific gravity of 1015 in six cases.

Two drugs were employed in this study; an extract of the whole root of Rauwolfia serpentina* and reserpine,† a pure crystalline alkaloid derived from this root. Both were taken 8-hourly by mouth. The nineteen subjects were each studied for a mean period of 47 weeks, every trial being divided into three periods. During the first period, which lasted for a mean of 17 weeks, a placebo was administered. During the second period which lasted for a mean of 21 weeks an active Rauwolfia preparation was given, and during the third period this was again replaced by a placebo, in most instances of identical appearance and taste: the average duration of this second placebo period was 11 weeks. In 7 subjects, as can be seen from the table, a complete second trial was carried out making a total of 26 trials in the 19 subjects.

* Raudixin, Squibb. † Serpasil, Ciba.

During the course of 16 trials repeated ballistocardiograms * were recorded on an average of 4·7 times while on placebo and 4·7 times while on a Rauwolfia drug in each trial, cardiac outputs being calculated according to the method of Tanner (1939). Although these records were not made under ideal basal conditions each patient was tested at the same time of day by the same observer after twenty minutes rest on the table.

Throughout the period of study each subject was seen by the same observer in the same room at the same time of day at weekly or fortnightly intervals. A supine blood pressure was recorded as soon as the subject lay down and again after five minutes rest, that reading, with the lower diastolic pressure, being used for the purposes of comparison in this study. Thereafter a standing blood pressure was recorded and symptomatic changes noted down. In Table I all the pressures while on placebo, both before and after the period on active drug, are averaged and compared to the average of all readings obtained during the period on rauwolfia. Because the effect of rauwolfia may be slow to appear and may continue for some time after the drug is withdrawn (Joiner and Kauntze, 1954), the blood pressures recorded for three weeks after the institution or cessation of rauwolfia treatment have not been included in this comparison.

Results

It is clear that the average blood pressure on treatment was considerably lower than the average control readings in 23 of the 26 trials, or in 16 of the 19 subjects. Comparison of the means in each individual trial by Student's t test showed that there was a statistically significant fall of the systolic pressure in 18, of diastolic in 21, and of both systolic and diastolic in 17 trials ($p=0·05$ or less) (Yule and Kendall, 1940). Moreover, the graphed results in each case showed that the lowest falls were often only obtained towards the end of the rauwolfia period at which time pressures were normal or near normal (less than 170/95) in 5 of the 13 severe and moderate cases and in 5 of the 6 mild cases. Postural hypotension was not observed.

No symptomatic improvement occurred that could definitely be ascribed to rauwolfia in this study. Symptoms possibly related to hypertension were present in 11 of the 19 subjects. Headache (7 cases) invariably improved on placebo and no further improvement was noted on rauwolfia. Angina (4 cases) was unaffected in 3 and was possibly worse in one. Dyspnœa, almost certainly of psychogenic origin was completely relieved by placebo and coincident psychotherapy in one case. In 3 patients it was aggravated and in 2 somewhat relieved during therapy.

Side effects appeared at widely different dosage levels. Some subjects were extremely uncomfortable on 0·75 mg. reserpine daily while one subject felt no symptoms on 6·0 mg. daily for a period of two months. They were reported in 10 subjects and although not dangerous they were sufficiently severe to limit the usefulness of the drug in 5 of these. The commonest symptoms were tiredness, sleepiness, depression, nasal obstruction and breathlessness. Most of these subjects " felt awful " on rauwolfia and felt, by contrast, extremely well when rauwolfia was replaced by placebo (in many cases identical in appearance and taste). In no case was there euphoria or a sense of well being observed which was not also obtainable with placebo. The rarer symptoms were insomnia (1 case), diarrhœa (1 case), nocturnal frequency (3 cases), increased appetite (1 case), increased thirst (2 cases) and disturbance of vision (1 case).

In addition to these subjective side effects a gain in weight was observed in 10 subjects during treatment and a steady weight loss due to dieting was temporarily arrested in a further two (Fig. 1) while the temporary appearance of œdema and a raised venous pressure in five led to the diagnosis of congestive cardiac failure.

There was no observable difference in the hypotensive action or side effects of raudixin and serpasil except in Case 19. In this subject 0·5 mg. serpasil produced shakiness and weakness of an intolerable degree with aggravation of angina, whereas 750 mg. raudixin daily produced no effects

* High-frequency resisted ballistocardiograph (Starr *et al.*, 1939).

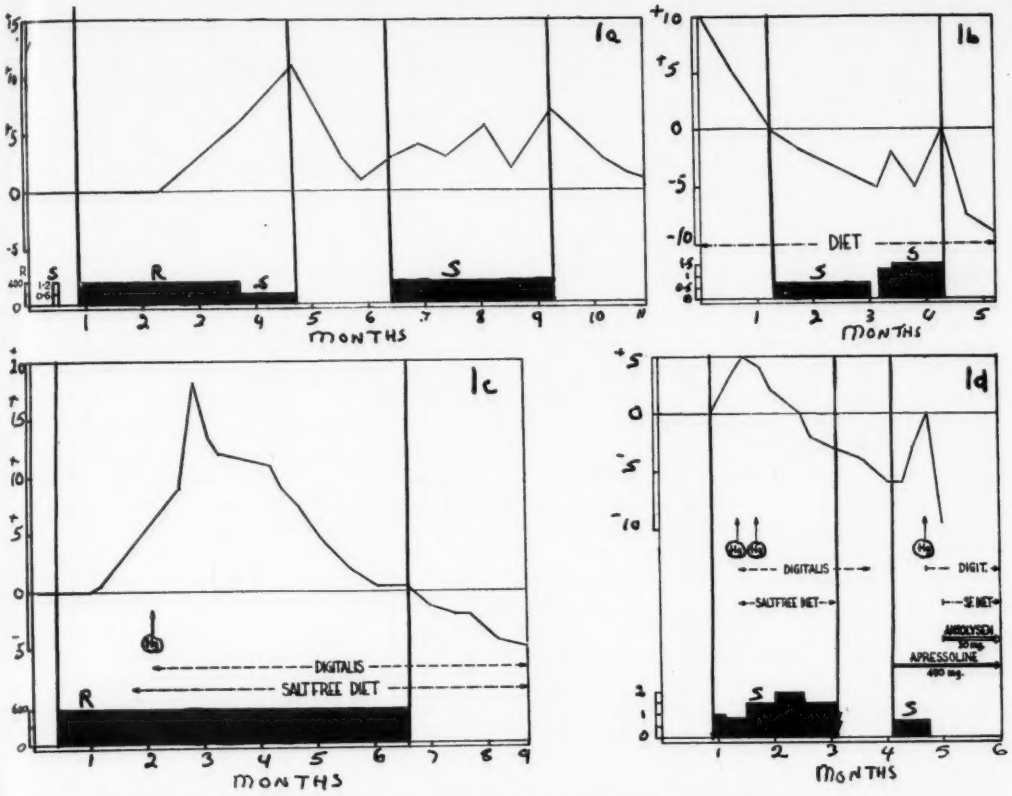

FIG. 1.—Illustrating weight changes in four cases while on Rauwolfia drugs. R=raudixin—total daily dose in mg. S=serpasil—total daily dose in mg. Hg=Mercurial diuretic.

GRAPH 1a. (Case 1). Note the rise in weight while on raudixin and serpasil in both trials and drop on withdral.

GRAPH 1b (Case 6). Note the temporary rise in weight when serpasil dose increased, and sudden drop on withdrawal. Reducing diet throughout.

GRAPH 1c (Case 2). Note marked weight gain on serpasil and rapid loss after institution of digitalis and salt-free diet.

GRAPH 1d (Case 7). Note the weight gain on serpasil and then weight loss with digitalis, mercury and salt-free diet in first trial. In second trial there is a rapid fall in weight following a single injection of mercury and withdrawal of serpasil.

whatever apart from a substantial lowering of blood pressure. The unpleasant effects of serpasil were abolished when this drug was replaced by placebo.

Observations of pulse rate and cardiac output were made during 16 trials. As in the case of blood pressure measurements the average of all readings obtained while under the influence of rauwolfia was compared to the average of all readings obtained while on placebo (Table I). Therapy resulted in a bradycardia in 14 trials with a corresponding increase in stroke volume and (within the errors of the method) a constant cardiac output in 12 of these. In two trials, however (Case 1, trial 2 and Case 19), there was an apparently significant fall in the resting cardiac output while on rauwolfia and in two others (Cases 3 and 5) the drug appears to have had no significant effect on these measurements.

Discussion

The results reported above confirm the almost universal view that a substantial reduction in blood pressure can be obtained by the administration of rauwolfia in many cases of essential hypertension. A worthwhile reduction of blood pressure was obtained in 16 of our 19 subjects while on treatment. That this was the result of the drug was borne out by the fact that pressures rose again within a month of withdrawal of rauwolfia in each case and in the 6 responsive subjects who received a second trial pressures were again lowered while on the drug. Moreover our results, so far as they go, confirm the conclusions of Moyer (1954) that rauwolfia is equally effective in both mild and severe cases. Like other workers (Wilkins, 1954; Hughes *et al.*, 1954) we found no difference in the therapeutic effectiveness or the incidence of side effects between the extract of whole root and the pure alkaloid except in the one subject who could only tolerate the former.

As may be seen from Table I, it is clearly not possible to lay down optimal dosage levels within any narrow limits. There was great variability from patient to patient both in the quantity of rauwolfia required to reduce the blood pressure and in the quantity tolerated before side effects became too severe. Nor was there any evidence of a constant toxic therapeutic ratio. While in some, normal pressures could be obtained with as little as 150 mg. raudixin or 0·8 mg. serpasil daily, others required as much as 6 mg. serpasil daily to achieve this result. The dose used, therefore, is frequently the result of a compromise in which the desirability of attaining a normal pressure must be balanced against the extent of incapacity due to side effects.

Of special interest was the occurrence of an increase in weight in some subjects while on rauwolfia. It has been well known for some years and has been attributed by some to an increase in appetite (Hughes *et al.*, 1954; Ford and Moyer, 1953). That this was the only cause for the increase in weight seemed to us unlikely for several reasons. Firstly, only two of our subjects reported an increase in appetite, even on direct questioning. Secondly, the rapidity with which weight was gained on treatment and lost again thereafter seemed unlikely to be the result of increased nutrition alone (Fig. 1, a, b, and d). Thirdly, there was evidence in five cases of fluid retention in the form of raised venous pressure and ankle œdema (Table I) which could be readily abolished in each case by the administration of mercurial injections and a low salt diet. Finally, it is apparent that in some cases the administration of digitalis, mercurials, and a low salt diet obviously arrested, or actually reversed, the weight increase in those subjects in whom it was employed (Fig. 1, c and d). These observations in some of the earlier cases immediately suggested the possibility that the weight increase on rauwolfia might be due to heart failure and it was with this possibility in mind that subsequent cases were studied in greater detail.

Dyspnœa may be difficult to assess in individuals receiving rauwolfia drugs. Nasal obstruction may cause discomfort which is easily confused with respiratory dyspnœa and according to Winsor (1953, 1954) may even produce attacks similar to paroxysmal nocturnal dyspnœa in subjects receiving an evening dose. It was our opinion, however, that the dyspnœa reported in our cases was not solely the result of nasal obstruction. In each, the cardiac status was such as to make heart failure a distinct possibility. In none had there been any evidence of heart failure at the commencement of rauwolfia therapy and in all except Case 10 signs and symptoms of failure did not recur at its conclusion even when digitalis, mercury and low salt diet were discontinued. We concluded that a syndrome that was almost certainly due to heart failure had developed in 6 of our 19 cases while on rauwolfia treatment and that it had cleared up when this drug was withdrawn in 5 cases.

The mechanism whereby rauwolfia caused this temporary heart failure during its administration is not known. It has previously been shown in acute experiments in dogs and in man (Moyer, 1954; Moyer *et al.*, 1954; Sellers and Hafkenschiel, 1954) that the intravenous infusion of reserpine has no significant effect on cardiac output. In view of the fact that there seem to be several differences between the actions of rauwolfia in acute and long-term experiments it was thought that a study of output carried on over months might produce a different result. As can be seen from

TABLE I

INFLUENCE OF RAUWOLFIA ALKALOIDS ON BLOOD PRESSURE, CIRCULATION, AND FLUID BALANCE

Case	Sex	Age	Severity ***	Trial	Raudixin **	Serpasil **	Control B.P. average	Treatment B. P. average	Changes in B.P.	Control H.R. average	Treatment H.R. average	Control S.V. average	Treatment S.V. average	Control C.O. average	Treatment C.O. average	Weight gain on treatment	Weight loss after treatment	Effort dyspnœa	Œdema
1	M	40	3	1	400		228/148	184/108	−44*/−40*	70	60	44	59	3·14	3·54	+11	− 8		
				2		1·2	220/152	190/125	−30*/−27*	78	60	49	36	3·53	2·13	+ 4	− 6	+	
2	F	39	3	1	600		254/144	189/112	−65*/−32*	76	60	64	74	4·90	4·45	+17	− 4	+	+
				2		2·0	271/132	175/104	−96*/−28*	77	54	57	78	4·27	4·02	− 2	− 1		
3	F	40	2	1	300		193/127	139/96	−54*/−31*							0	0		
				2		2·0	184/125	152/101	−32*/−24	76	76	54	44	3·60	3·34	0	0		
4	F	63	1	1	300		196/103	160/81	−36*/−22*							+ 3	0		
5	F	51	1	1	800		198/124	183/100	−15*/−24*	72	70	62	59	4·72	4·15	+12	− 3		
6	F	41	1	1		1·5	191/127	133/81	−58*/−46*	81	59	62	77	4·11	4·46	+ 5	−10		
7	M	41	3	1		1·5	197/136	182/101	−15/−35*	82	60	39	51	3·07	3·07	+ 5	− 3		+
8	F	60	2	1	300		202/109	177/90	−25*/−19*							+17	− 1	+	
				2		0·8	188/107	157/83	−31*/−24*	51	47	53	63	2·68	2·02	0	− 7		
9	M	67	1	1	150		193/109	157/69	−36*/−40*							+ 5	− 2		
10	M	49	3	1		1·25	192/110	167/74	−25*/−36*								0	+	+
11	F	49	3	1	750		256/143	224/138	−32/−5									+	+
12	F	60	2	1		2·0	214/111	192/92	−22/−19*	69	57	35	41	2·41	2·42	+ 8		+	
13	F	57	1	1	200		179/108	183/101	+4/−7							0	0		
				2	600		184/103	180/109	−4/+6	61	47	42	50	2·62	2·33	0	0		
14	F	49	3	1	450		201/116	179/94	−22/−17*							+19	− 7	+	+
				2		3·0	207/117	194/105	−13*/−12*	71	61	57	62	4·05	3·77	+ 5	− 4	+	
15	F	65	2	1		1·5	185/109	157/97	−28*/−12*	76	66	44	46	3·35	3·07	0	0		
16	F	50	2	1		1·0	220/113	202/95	−18/−18	73	64	45	54	3·07	3·58	0	− 6		
17	M	48	1	1	750		156/115	138/100	−18*/−15*							−	−		
				2		6·0	153/108	130/88	−23*/−20*	67	57	54	54	3·59	3·09	0	0		
18	F	55	2	1		0·8	204/118	191/100	−13/−18*							−	−		
19	F	44	3	1	750		239/149	190/111	−49*/−38*	76	62	51	47	3·92	2·90				

* P<0·05† ** Total daily dose in mg. *** 1=Severe; 2=Moderate; 3=Mild. H.R.—Heart rate.
S.V.=Stroke volume in mils. C.O.=Cardiac output in litres/min.

Table I, however, the cardiac output was substantially unchanged in all but two trials, in which a fall occurred. Increased cardiac output therefore was not the cause of heart failure.

An explanation, however, which merits consideration is that rauwolfia may have caused in some cases a fluid retention that was capable of precipitating heart failure in those subjects with incipient decompensation. This hypothesis would be consistent with the reported antidiuretic effect of reserpine in animals (Gaunt *et al.*, 1954) and would explain the significant weight gain observed in the absence of failure by other workers and in our Cases 5, 6, and 9. Whatever its cause, the occurrence of failure in 6 of our 19 cases while receiving rauwolfia is an observation of some significance. It suggests that this drug, at least in the presence of a damaged myocardium, should be given with caution, and that an increase in weight and signs and symptoms of failure should be looked for with special care in these subjects.

Summary and Conclusions

An extract of the whole root of Rauwolfia serpentina or the alkaloid reserpine were capable of producing a substantial fall in the blood pressure in 16 of 19 subjects with essential hypertension.

The pressure was reduced to normal or near normal levels in 10 of the 19 subjects.

The optimal dose varied from 0·75 to 6·0 mg. serpasil and 150–800 mg. raudixin daily. Any attempt to lay down a dosage within narrower limits would lead to under treatment in some cases and gross toxicity in others.

The side effects are briefly discussed. In most subjects there was a significant increase in weight and in six subjects temporary heart failure developed while on the drug.

It is suggested that rauwolfia drugs may have an anti-diuretic effect in man which may cause an increase in weight due to fluid retention. Congestive cardiac failure may be precipitated in those with previously damaged hearts.

Whatever the actual mechanism of failure, it is clearly a possible hazard in subjects of poor cardiac status who are treated with rauwolfia drugs. Rauwolfia treatment in these subjects should be undertaken with some caution.

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CARDIAC PAIN IN ASSOCIATION WITH MITRAL STENOSIS AND CONGENITAL HEART DISEASE

BY

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The association of angina pectoris with mitral stenosis has interested cardiologists for many years. The first reference seems to be that of Nothnagel (1891) who found anginal pain in 18 per cent of his patients with mitral stenosis. There have been many case reports since that time of angina pectoris occurring in young subjects with mitral stenosis (Graham Steel, 1906; Hirschfelder, 1910; Sternberg, 1923; Telia, 1925; Hochrein, 1930; Scherf and Goldhammer, 1933; Parker and Weiss, 1936), and in a number of instances normal coronary arteries were revealed at necropsy. For example Blackford (1940) reported two such cases with severe mitral stenosis and normal coronary arteries and found seven previously reported cases in which the results of necropsy were available, and 25 other case reports since 1923. Burgess and Ellis (1942) considered that true angina pectoris was rare with mitral stenosis and confined to older patients, and discussed so-called "hypercyanotic angina" occurring in long attacks unrelated to effort. Levine and Kauvar (1942) studied 38 patients with mitral stenosis and angina pectoris: three were under the age of 40 years, and women predominated over men in the proportion of 2:1. The average age of onset of angina was 50 years for the women and 54 years for the men. The incidence of angina pectoris among 741 patients with mitral stenosis was 2·6 per cent. In sixteen of their patients the results of necropsy were available; in three of these the coronary arteries were normal. Significant disease of the coronary arteries was found post-mortem in only 5 per cent of 314 cases of mitral stenosis. They concluded that in the majority of such patients mitral stenosis and coronary artery disease merely coexist. This has been the general opinion since that time, and is quoted in most textbooks.

The impression that aortic incompetence is the only valvular lesion commonly associated with angina pectoris in young subjects, seems to date from papers by White and Mudd (1927) and by Schwartz (1927). Most of the thirteen patients mentioned by these authors had mitral valve disease as well, and there was no post-mortem confirmation.

References to the occurrence of angina pectoris in patients with congenital heart disease are more scanty. Aortic stenosis has only recently been considered a relatively common congenital condition (Campbell and Kauntze, 1953), but the association of angina pectoris with this lesion is well recognized, and it occurred in 11 of the 40 patients reported by these authors. Friedberg (1949) put the incidence of angina of effort in patients with aortic stenosis at 10–20 per cent, perhaps more if specific enquiry is made for the symptom, and quoted his own earlier work (Friedberg and Horn, 1939) demonstrating acute myocardial damage and normal coronary arteries at necropsy in patients with aortic stenosis who had died suddenly. Isolated cases have been reported of angina pectoris occurring in patients with atrial septal defect (Bedford *et al.*, 1941; Viar and Harrison, 1952), the tetralogy of Fallot (Blackford, 1930; Dow *et al.*, 1950), pulmonary stenosis (Lowance *et al.*, 1948; Wood, 1950; Abrahams and Wood, 1952), transposition of the great vessels (Astley and Parsons, 1952), and Eisenmenger's complex or patent ductus arteriosus (Viar and Harrison, 1952).

The association of angina pectoris with pulmonary hypertension was first described by Vaquez

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and Giroux (1908), who coined the phrase "angine pulmonaire hypercyanotique" to describe a clinical syndrome associated with pulmonary vascular abnormalities and lung disease. Posselt (1908), Frugoni (1911), Arillaga (1913), and Engelen (1923) reported similar cases. Brenner (1935) described a boy, aged 11 years with anginal pain, in whom necropsy revealed primary pulmonary arteriosclerosis and gross hypertrophy of the right ventricle, and suggested that the pain was due to myocardial anoxia associated with arterial anoxæmia. Brill and Krygier (1941) found that chest pain of anginal type had been described in 4 of 20 reported cases of primary pulmonary hypertension including one of their own, and suggested that it might be due to coronary insufficiency associated with diminished systemic blood flow through an obstructed pulmonary circulation. Wood (1950) found angina in three of six patients with idiopathic pulmonary hypertension. Viar and Harrison (1952) described six patients with chest pain associated with pulmonary hypertension, three of them with emphysema, one with atrial septal defect, one with mitral stenosis, and one with massive pulmonary embolism: necropsy in three showed normal coronary arteries. They described the pain as identical clinically with angina pectoris but perhaps lasting longer, often accompanied by dyspnœa, and relieved by the administration of oxygen or aminophylline but not by trinitrin. They suggested that the pain was due to distension of the pulmonary artery.

A number of cases were encountered of classical angina of effort in young subjects with congenital heart lesions or with mitral stenosis. It was decided to investigate both these groups of patients, hoping that the one might throw some light on the other. The congenital group provides such a wide range of variation in blood flow, in pressures in various chambers and vessels, and in arterial oxygen saturation, that it was hoped some explanation might be found for cardiac pain occurring in the absence of coronary artery disease.

Mitral Stenosis

A brief report of the conclusions reached in regard to patients with mitral stenosis suffering from angina pectoris has been given by Wood (1954). The patients selected were those giving a classical story of angina of effort identical with that given by older patients with coronary artery disease, except that the chest pain was often accompanied or preceded by breathlessness, and when provoked by effort sometimes persisted for as long as ten minutes before being relieved by rest. The many other types of chest discomfort found in patients suffering from mitral stenosis have been excluded.

Amongst 400 patients with mitral stenosis, angina pectoris occurred in 34 (8 %), and the details are shown in Table I. The female to male ratio was 4·7:1, and the average age 37 years for the women and 33 years for the men. The age and sex incidence of uncomplicated ischæmic

TABLE I

Incidence of Angina Pectoris in Patients with Mitral Stenosis

Group	Condition	Number in group	Angina under the age limits*	Angina over the age limits*	Angina at all ages
I	Mitral stenosis (operation series)				
	With severe pulmonary hypertension ..	29	4		
	Uncomplicated severe stenosis	37	4		
	Mild or moderate stenosis	34	—		
	All patients in this group..	100	8 (2 A.F.)	1 (A.F.)	9
II	Mitral stenosis, normal rhythm	100	7	4	11
III	Mitral stenosis, auricular fibrillation	100	2	7	9
IV	Mitral stenosis, with some aortic incompetence	100 (30 A.F.)	4	1	5
	Mitral stenosis, all patients reviewed	400	21 (5%)	13 (3%)	34 (8%)

A.F. Auricular fibrillation.

* In men, under 35 years of age; in women, under 37 years of age.

heart disease studied at the same hospital over the same period of time (Stuckey), 1955, rendered it most unlikely that coronary atherosclerosis played a significant part in the production of cardiac pain in men aged under 35 years or in women under 37 years.

There were 21 patients under these age limits with mitral stenosis and angina pectoris, and some details are recorded in Table II. The pulse was of small volume in 19: the blood pressure was normal or low, with two exceptions in which the systolic pressure was 170 mm. Hg. Hæmoglobin values were within the normal range.

TABLE II

PATIENTS WITH ANGINA PECTORIS AND MITRAL STENOSIS

Case No.	Age	Sex	Diagnosis	Rhythm	Systemic B.P.	P.A. pressure	L.A. pressure	Cardiac output	Pulm. resistance	Valve size
1	32	F	M.S. (T.S.), P. H.* ..	N.	170/80	90/45	15	2·3	21	Slit 0·5 cm.
2	27	F	M.S. (T.I.), P. H. ..	N.	120/80	90/40	20	2·7	17	Slit 0·6 cm.
3	36	F	M.S., P. H.	N.	110/76	90/45	30	2·0	15	Slit 1·0 cm.
4	34	F	M.S. (M.I.), P. H. ..	A.F.	88/50	92/48	25	3·7	9	Slit 1·0 cm.
5	27	F	M.S. (A.I.), P. H. ..	N.	90/50	55/30	20	4·7	3·5	0·5 cm. long
6	33	M	M.S. (M.I.), P. H. ..	A.F.	120/70	50/27	—	4·8	—	Slit 2·0 cm.
7	19	F	M.S. severe	N.	100/70	—	30	—	—	0·6 by 0·3 cm.
8	28	F	M.S. (A.I.)	N.	105/55	40/20	20	5·5	2	0·75 by 0·5 cm.
9	30	M	M.S., P. H.	N.	90/60	75/40	18	3·5	10	1·0 by 0·5 cm.
10	32	F	M.S. (?A.I.)*	N.	140/100	35/12	12	2·5	3·5	Not known
11	26	F	M.S. severe	N.	95/60	43/18	20	2·6	4·6	0·75 by 0·25 cm.
12	30	F	M.S.*	N.	120/75	16/3	5	4·3	1	Not known
13	36	F	M.S. (?A.I.)	N.	—	No catheter				
14	31	F	M.S.	N.	—	No catheter				
15	33	M	M.S., M.I., P. H. ..	A.F.	170/105	No catheter				0·6 cm. diam.
16	35	F	M.S., P. H.*	A.F.	100/60	35/12	10	2·8	6	
17	34	M	M.S. (A.S., A.I.) ..	N.	95/65	62/25	25	4·6	4·3	
18	36	F	M.S. (A.I.)	N.	120/80	50/32	24	5·0	3·2	
19	27	F	M.S. A.I.	N.	150/75	No catheter				
20	19	M	M.S. A.I. (T.S., P.S.) ..	N.	120/90	No catheter				Less than tip of fifth finger
21	23	F	M.S., P. H.	N.	135/80	100/45	12	3·7	13	0·8 by 0·4 cm.

N. Normal sinus rhythm. A.F. Auricular fibrillation. P.H. Pulmonary Hypertension.
Pressures in mm. Hg. Cardiac output in l./min. Pulmonary resistance in arbitrary units.
* These patients had a tendency to faint on exertion.

Generalized cardiac enlargement on radiological examination was not characteristic, and was noted in only four patients. In two the heart was considered to be small. The right ventricle appeared to be enlarged in twelve patients, and the main pulmonary artery in ten. The electrocardiogram showed various degrees of right ventricular preponderance in thirteen patients, and was normal or balanced in the remainder.

Seven patients had severe pulmonary hypertension, with a high pulmonary resistance and a low cardiac output at rest. Of eight other patients who were catheterized, the cardiac output was low in six and within normal limits in only two. Very low figures for the cardiac output were found both among those with and without pulmonary hypertension.

No direct measurements of cardiac output on exertion were made, but in six patients changes in the pulmonary artery and pulmonary capillary pressures were observed during exercise. If pulmonary capillary pressure is taken to represent left atrial pressure (Epps and Adler, 1953) and if the pulmonary resistance remains constant (Gorlin *et al.*, 1951), the cardiac output on exertion may be calculated from the equation:

$$\text{Pulmonary resistance (units)} = \frac{\text{P.A. pressure} - \text{L.A. pressure (mm. Hg)}}{\text{Cardiac output (l./min.)}}$$

In five of the six patients the cardiac output so calculated showed an increase from the resting level of less than 50 per cent.

The size of the stenosed mitral orifice was estimated at operation or at necropsy in 13 patients. The area was estimated to be less than 0·5 sq. cm. in 11 and about 1 sq. cm. in the remaining two. Angina pectoris was completely relieved after operation in all cases.

The occurrence of angina pectoris in patients with mitral stenosis could thus be correlated with (1) the severity of the stenosis, as judged clinically or as estimated at operation or at necropsy; and (2) low cardiac output at catheterization, (suggested clinically by a pulse of small volume, low systemic blood pressures, and cold vasoconstricted extremities) which was associated with severe mitral stenosis or severe pulmonary hypertension or both.

Other Rheumatic Valvular Lesions

One hundred consecutive patients with predominant aortic incompetence were reviewed for the occurrence of angina pectoris. The aortic valve lesion was considered to be of rheumatic origin in all, and any involvement of the mitral valve was judged to be slight. Those with systemic hypertension were excluded, as were patients with syphilitic aortitis or valvulitis. Nine patients suffering from angina pectoris were found, and their age incidence corresponded closely with that of uncomplicated coronary heart disease, the youngest being 49 years of age.

Among 40 patients with pure mitral incompetence presumably of rheumatic origin there were none suffering from angina pectoris. Tricuspid valve stenosis was thought to be the predominant lesion in one patient, a woman aged 40 years, who had suffered from angina of effort for three years. Unfortunately the clinical diagnosis was not proven by catheterization or necropsy.

The common association of angina pectoris with aortic stenosis is well known. Rheumatic aortic stenosis is often combined with a lesion of the mitral valve. Isolated aortic stenosis in young subjects was considered to be more often congenital in origin, and these patients are considered in the next section.

Congenital Heart Disease

The same criteria for the diagnosis of angina pectoris and the same age limits were used as for the patients with mitral stenosis. There were 448 consecutive patients with a congenital heart lesion available for review, and there were an additional 26 patients with isolated aortic or subaortic stenosis in whom the murmur had been discovered in infancy or early childhood and who showed no evidence of rheumatic disease. Many of the latter group were included in the series reported by Campbell and Kauntze (1953). Six patients suffering from primary pulmonary hypertension were also included.

Angina pectoris occurred in 23 (4·8%), and these patients fell into three main groups.

(1) Aortic stenosis (6 of 26 patients).

(2) Severe pulmonary stenosis (6 of 38 patients).

(3) Pulmonary hypertension, either primary (2 of 6 patients), of complicating a shunt with left to right blood flow or with a balanced circulation (6 of 24 patients.)

In the remaining three patients with angina pectoris the diagnosis was not established with certainty despite full investigation, but two of them probably suffered from infundibular pulmonary stenosis with reversed inter-atrial shunt, and the third from pulmonary hypertension complicating an atrial septal defect. There was no history of angina in 183 patients with uncomplicated left-to-right shunts, in 79 patients with mild or moderate pulmonary stenosis, in 30 patients with reversed shunts due to severe pulmonary hypertension, and in 83 patients with morbus coeruleus (mostly Fallot's tetralogy).

Some of the findings in the twenty patients with angina pectoris in whom an exact diagnosis was made are shown in Table III. Overwhelming female preponderance was found amongst those with pulmonary hypertension (Wood, 1952). The pulse was of small volume in fifteen patients and the systemic blood pressures were mostly in the low normal range. Hæmoglobin values were

normal or raised. It is interesting to note the value of 140 per cent in Case 10, a patient with severe infundibular stenosis as an isolated lesion proven at necropsy. Similar high hæmoglobin values have been found in some patients with primary pulmonary hypertension (Wood, 1952). Generalized cardiac enlargement of more than slight degree was found on radiological examination in only three patients, and there were no characteristic changes in the electrocardiogram at rest.

TABLE III

PATIENTS WITH ANGINA PECTORIS AND CONGENITAL HEART DISEASE

Case No.	Age	Sex	Diagnosis	Pulse	Systemic B.P.	Hb.	R.V. pressures	P.A. pressures	Cardiac output	Resistance	Arterial O_2 satn. %
1	27	F	Primary pulmonary hypertension* ..	Small	105/80	13·3	108/6	117/60	4·3	20	95
2	24	F	Primary pulmonary hypertension* ..	Small	100/80	13·1	50	63	5·3	12	93
3	31	F	P.D.A. and pulmonary hypertension* ..	Normal	120/70	14·0	130/5	85	4·0	21	85
4	23	F	P.D.A. and pulmonary hypertension* ..	Normal	135/60	12·0	—	66	—	—	95
5	13	F	P.D.A. and pulmonary hypertension ..	Normal	120/65	15·4	115/2	115/75	—	>13	83
6	30	F	A.S.D. and pulmonary hypertension ..	Small	105/65	17·5	100/0	100/55	2·7	12	95
7	28	F	A.S.D. and pulmonary hypertension* ..	Small	100/75	18·2	30	58	2·5	11	88
8	33	F	A.S.D. and pulmonary hypertension ..	Small	115/85	14·7	52	72	3·5	20	84
9	27	F	Pulmonary valve stenosis	Small	118/60	80%	175/3	2	<4·0	—	95
10	23	F	Pulmonary valve stenosis	Small	120/80	—	Not catheterized				
11	20	M	Infundibular stenosis ..	Small	110/50	140%	15(?)	5	1·6	—	94
12	28	M	Infundibular stenosis* ..	—	90/55	105%	60/4	21/1	4·6	—	92
13	26	F	Pulmonary stenosis and reversed inter-atrial shunt*	Small	130/90	17·5	165/5	2	—	—	82
14	10	F	Pulmonary stenosis and reversed inter-atrial shunt	Small	80/55	13·3	125/15	17/10	2·8	—	82
15	24	F	Aortic stenosis	—	120/90	—	Not catheterized				
16	14	M	Aortic stenosis	Small	105/80	—	Not catheterized				
17	18	M	Aortic stenosis	Small	130/90	—	Not catheterized				
18	29	M	Aortic stenosis	Small	120/100	—	Not catheterized				
19	27	F	Subaortic stenosis ..	Small	—	—	Not catheterized				
20	26	F	Aortic stenosis	Small	100/80	—	Not catheterized				

Hæmoglobin values in g. per 100 ml., or as percentage of normal (Haldane). All pressures in millimetres of mercury. Cardiac output in litres per minute. Resistances in arbitrary units.

* These patients had a tendency to faint on exertion.

The arterial oxygen saturation was normal in eight patients and low (82–85%) in five, presumably because of some right-to-left shunting. Much lower figures were of course found in patients with cyanotic forms of heart disease who did not have cardiac pain. The cardiac output at rest was low in seven of the nine patients in whom it was estimated. From observations during exercise in one patient the calculated cardiac output increased less than 20 per cent above the resting level.

Angina pectoris did not occur in patients with uncomplicated left-to-right shunts, with pulmonary stenosis of mild or moderate degree, or with most cyanotic forms of congenital heart disease. It is important to note the difference in incidence of angina pectoris in patients with left-to-right shunts with pulmonary hypertension, and in those with the same lesions complicated by *severe* pulmonary hypertension that had produced free blood flow from the right to the left side of the

heart. In the latter group of patients levels of pulmonary blood pressure were higher, right ventricular work and right ventricular hypertrophy were greater, the size of the heart was increased, and levels of arterial oxygen saturation were lower; yet angina pectoris did not occur. The conclusion is that these features are not essential for the production of cardiac pain. It is suggested that the essential difference between these two groups is the establishment of the reversed shunt, whereby on exertion blood returning to the right side of the heart can be transferred more easily to the left side, and the cardiac output increased thereby in a relatively normal fashion. The obstruction (pulmonary arteriolar vasoconstriction or sclerosis) is by-passed by blood flowing in a reverse direction through the shunt. Similar reasoning may be applied to patients with severe pulmonary stenosis and with Fallot's tetralogy except that in the latter group dextraposition of the aorta is present as well as a septal defect which can act as a by-pass. In the other two groups with a high incidence of angina pectoris, namely primary pulmonary hypertension and aortic stenosis, the obstruction cannot normally be by-passed, but the possibility of making an artificial ductus arteriosus in the treatment of primary pulmonary hypertension has been considered (Wood, 1952).

There were two features common to the patients with cardiac pain; firstly, an obstruction to the circulation of the blood, either severe organic stenosis of the aortic valve, the pulmonary valve or infundibulum, or obstruction in the pulmonary arterial tree associated with pulmonary hypertension; and secondly, evidence of a low cardiac output both on clinical grounds and at catheterization.

Post-Mortem Examination

The results of necropsy were available in eleven patients who had suffered from angina pectoris during life. Four had predominant mitral stenosis (Cases M.S. 1, 2, 15, and 20), two primary pulmonary hypertension (Cases C.H.D. 1 and 2), one severe infundibular stenosis (Case C.H.D. 11) and one severe aortic stenosis (Case C.H.D. 17). There were three additional patients who had suffered from angina pectoris, a woman, aged 33 years, with predominant mitral stenosis, and two men, aged 35 and 44 years, with severe aortic stenosis.

In all these patients at necropsy the coronary arteries appeared patent and normal, and the aorta showed little or no atheroma.

The Electrocardiogram on Exercise

Scherf and Goldhammer (1933) reported changes in the electrocardiogram suggestive of myocardial ischæmia during an attack of anginal pain at rest in a woman with mitral stenosis. Howarth and Lowe (1953) published one record showing changes in lead V1 on exertion in a patient with primary pulmonary hypertension.

Exercise tests were carried out on 33 patients in all, using the method described by Wood *et al.* (1950) and examples are shown in Fig. 1–4. The record in Fig. 3 has been published in part by Wood (1954). The twelve standard leads were recorded in most instances, both at rest and after exercise. There were fifteen control patients, eleven with mitral stenosis and four with congenital heart disease, who did not suffer from angina pectoris. Non-specific changes noted in the electrocardiogram were increase in the amplitude of the P and T waves. Sometimes a T wave that was flat or inverted at rest became upright on exertion. Two control patients showed slight changes suggestive of myocardial ischæmia on effort, of the type described below. One was a woman, aged 42 years, with both mitral and aortic stenosis, who did complain of tightness across the chest on hurrying, but had not been included among the positive cases because she insisted that it was not pain, and this had been used as a differential point. The other patient had severe pulmonary infundibular stenosis with a right ventricular systolic pressure of 100 mm. Hg and a cardiac output of 3·3 litres a minute at rest.

There were 18 patients who suffered from angina pectoris, 5 with mitral stenosis and 13 with

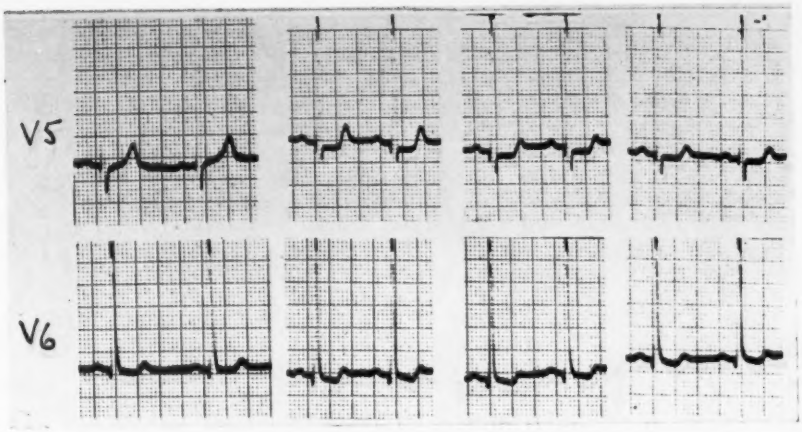

FIG. 1.—Exercise test in a man, aged 42 years, with aortic stenosis who had suffered from angina pectoris for ten years. (A) At rest. (B) During exercise. There was well-marked flat depression of the S–T segment in leads V5 and V6 with diminution or obliteration of the T wave, best seen in (C) taken 5 minutes after exercise, which produced anginal pain lasting 3 minutes in this patient. (D) Ten minutes after exercise.

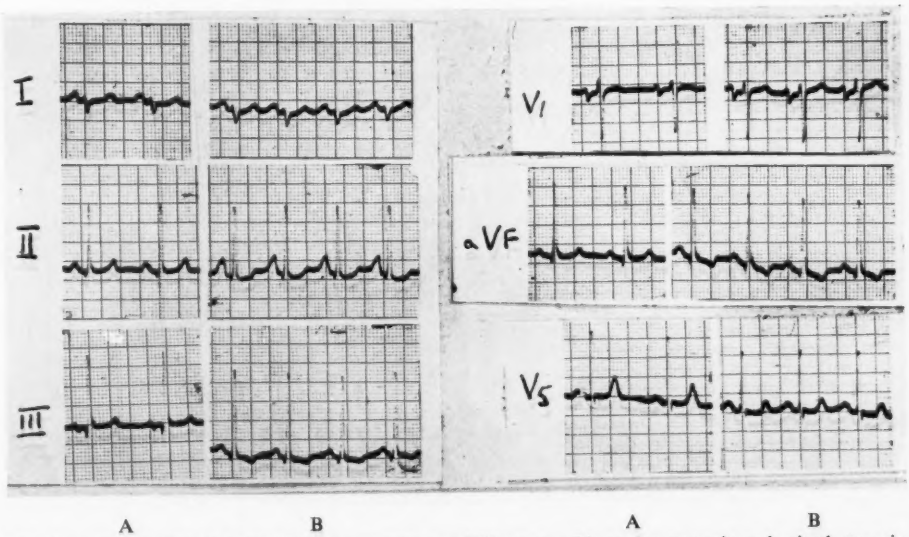

FIG. 2.—Exercise test in Case M.S. 10, a woman, aged 32 years, with angina pectoris and mitral stenosis. Slight aortic incompetence was present but no pulmonary hypertension. (A) At rest. (B) After exercise. There was slight sagging of the S–T segment with considerable reduction in the height of the T wave in leads V4 and V5, the same changes being reflected more strongly with complete inversion of the T wave in leads aVF, III, and II. The T wave in lead V1 was more upright after exercise. The test produced transient faintness but no pain in this patient. Blood pressure levels showed no significant alteration.

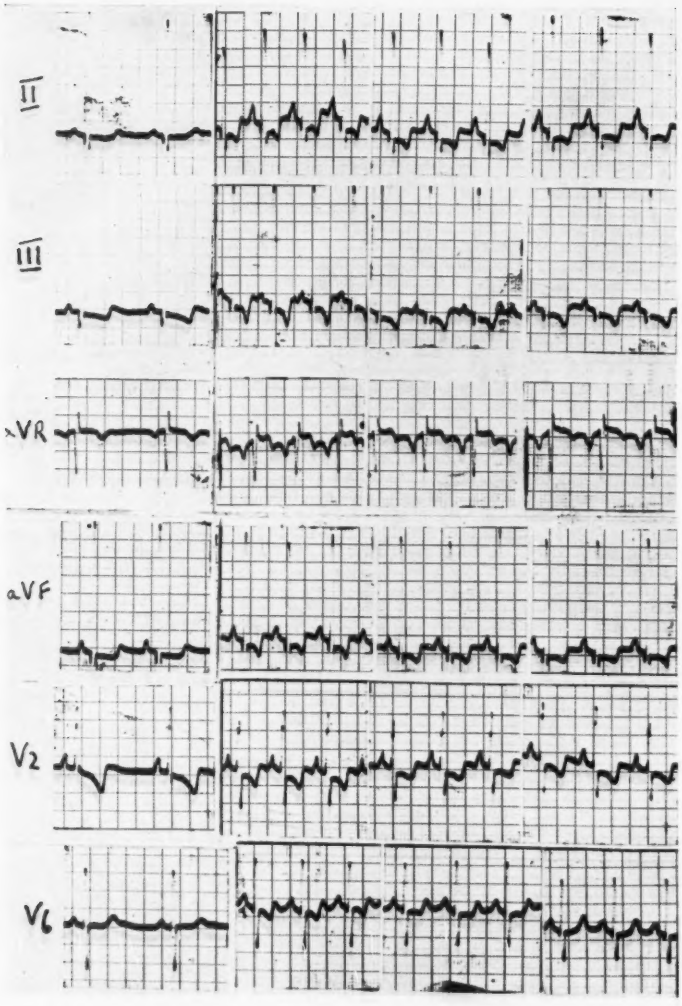

FIG. 3.—Exercise test in Case M.S. 21, a woman, aged 23 years, with mitral stenosis and severe pulmonary hypertension who suffered from angina pectoris. (A) Resting. (B) Two minutes, (C) 4 minutes, and (D) 6 minutes after exercise. There was flat elevation of the S–T segment and obliteration of the normally inverted T wave in lead aVR best seen at 4 minutes after exercise, and depression of the S–T segment and deep T wave inversion in leads II, III, and aVF. The pattern in these leads was abnormal at rest, making interpretation of the changes difficult. There was depression of the S–T segment and partial inversion of the T wave at 2 minutes and 4 minutes in lead V6, the only left ventricular surface lead, with return to the normal resting pattern at 6 minutes. There was less inversion of the T wave in lead V2 after exercise than at rest. The test produced anginal pain in this patient.

congenital heart disease. On exercise, changes in the cardiogram consistent with myocardial ischæmia were found in 7, suggestive changes of lesser degree in 5, and no significant change in 6 patients. All the latter had grossly abnormal records at rest, and this made it difficult or impossible to recognize significant changes after exercise.

Changes in the cardiogram indicating mycardial ischæmia were best seen in leads II, III, and aVF, and in *left* ventricular surface leads (V4–V7), even in patients with marked right ventricular preponderance in the cardiogram. Elevation of the S–T segment and obliteration of the normally inverted T wave in lead aVR may also be an ischæmic pattern. In right ventricular surface leads the tendency was for T waves previously inverted to become upright after exercise, and for the S–T segment to move in the same direction (Fig. 4); these changes were found in seven patients with marked right ventricular preponderance in the cardiogram at rest.

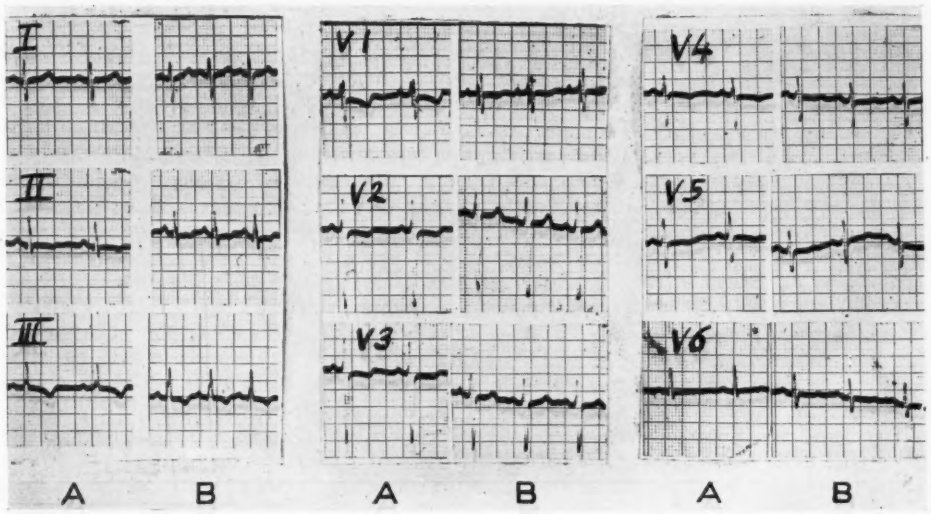

FIG. 4.—Exercises test in a woman, aged 47 years, who had suffered from primary pulmonary hypertension and angina pectoris. (A) Resting. (B) After exercise. There was slight S–T depression in lead II on effort. The T waves in leads V1–V5 inverted at rest became upright after exercise, and the S–T segments depressed at rest were isoelectric on exertion. Similar changes were found in right ventricular surface leads in a number of patients with angina pectoris and conditions associated with marked right ventricular preponderance, but did not occur in the controls. There is no true left ventricular lead shown: perhaps lead V7 or V8 would have been more useful.

In two patients in whom well-marked changes in the cardiogram occurred on exertion, trinitrin was given in full dosage before exercise. Exactly the same ischæmic changes were seen on exercise, and these took longer to disappear with rest. The blood pressure was estimated by the cuff method in eight patients before and after exercise sufficient to induce anginal pain, and the pressures after exercise were always at or above the resting level.

DISCUSSION

The ages of the patients discussed in this paper make it unlikely that coronary artery disease played a significant part in producing cardiac pain. This was confirmed by the absence of evidence of coronary artery disease in eleven patients at necropsy. Undoubtedly in older patients with less

severe mitral or aortic stenosis, coronary atherosclerosis may coexist and may play a contributory part in causing myocardial ischæmia on exertion.

Low arterial oxygen saturation with accompanying central cyanosis does not seem to be an important factor in producing cardiac pain. Most of the patients with angina pectoris had a normal arterial oxygen saturation, and in the six with potentially reversible shunts, the arterial oxygen saturation was 82 per cent or more at rest. Angina pectoris was not encountered among 83 patients with cyanotic forms of congenital heart disease nor among 30 with severe pulmonary hypertension and reversed shunts. The term hypercyanotic angina is best restricted to the group originally described by Vaquez and Giroux (1908).

Increased mass of cardiac muscle is probably not an important factor. Generalized cardiac enlargement of more than slight degree on radiological examination was uncommon in the patients with cardiac pain. In a number of them the heart appeared to be well within normal limits for size.

Evidence has been presented that myocardial ischæmia occurs on exertion in these patients with angina pectoris, and that the ischæmic changes in the electrocardiogram are best seen in left ventricular surface leads even in patients with marked right ventricular hypertrophy. Cardiac pain and rather similar changes in the cardiogram occur in patients with massive pulmonary embolism (Currens, 1942; Wood, 1948), and it is interesting to compare the myocardial lesions *post mortem* in this condition (Dack *et al.*, 1949; Currens and Barnes, 1943) and in aortic stenosis (Friedberg and Horn, 1939). In both conditions the myocardial lesions were subendocardial, focal, and disseminated, and greater in the left ventricle than in the right. The suggestion is that, in these conditions and in the patients discussed in this paper, those parts of the myocardium at the periphery of the normal coronary arterial tree and furthest removed from the source of blood supply will be affected by ischæmia first and most severely. The left ventricle would thus suffer as much as the right ventricle.

The important correlation of cardiac pain in patients with mitral stenosis or congenital heart disease is with a low cardiac output. It has been shown by a number of observers (Bayliss *et al.*, 1950; Draper *et al.*, 1951; Ball *et al.*, 1952) that in patients with severe mitral stenosis the cardiac output is low at rest and does not approach normal levels on exertion. The same probably applies to severe grades of aortic stenosis, pulmonary stenosis, and pulmonary hypertension. The coronary blood flow normally constitutes 4–5 per cent of the cardiac output at rest (Gregg, 1950), and the proportion may rise to 12–15 per cent after exercise, after administration of adrenaline, or in shock (Eckenhoff *et al.*, 1947). It is probable that this figure approaches the maximum proportion of the cardiac output that can be diverted into the coronary arterial tree while other essential parts of the circulation are maintained. When the cardiac output cannot increase adequately on exertion, the coronary blood flow may be too small for the demands of the myocardium, especially when the cardiac work is greatly increased by an obstruction to the circulation. The increased cardiac work involved for instance in aortic stenosis has been pointed out by Evans (1918).

The basic pathological condition in these patients is thus an obstruction to the circulation. This may be either an organic stenosis of the aortic, mitral, pulmonary, or tricuspid valves or of the infundibulum of the right ventricle, or obstruction in the pulmonary circuit associated with severe pulmonary hypertension (pulmonary arteriolar vasoconstriction or sclerosis).

In many of the patients discussed in this paper two or more obstructive lesions were present, for example, among those with mitral stenosis there was pulmonary hypertension in 6 cases, aortic stenosis in one, and tricuspid stenosis in two, one of these having pulmonary hypertension as well and the other pulmonary stenosis as well (see Table II). The effect of such multiple obstructions to the circulation of the blood on the ability of the cardiac output to increase normally on exertion is probably additive.

The patients described in this paper could be included in the all-embracing term "coronary insufficiency" as used by Masters and others, but in themselves form a compact clinical group with identical functional disturbance and well-known basic pathology, and so merit separate description.

Summary and Conclusions

Of 400 patients suffering from mitral stenosis, angina pectoris (angina of effort) occurred in 34 (8·5%), of whom 21 were aged under 37 years in the case of women, and under 35 years in the case of men. Of these 21 patients, seven had marked pulmonary hypertension and in the remainder the mitral stenosis was severe.

Among 480 cases of congenital heart disease, angina pectoris occurred in 23 patients under the age limits mentioned (4·8%). These fell into three main groups; aortic stenosis, severe pulmonary stenosis, and pulmonary hypertension, either primary or complicating a left-to-right or balanced shunt.

There was no evidence of coronary artery disease *post mortem* in eleven of these patients with mitral stenosis or congenital heart disease who had suffered from angina pectoris during life.

Exercise tests were carried out on 33 patients. Changes in the electrocardiogram on exercise indicating myocardial ischæmia were found in 12 of 18 patients with angina pectoris, and slight changes in only 2 of 15 controls. The changes were best seen in left ventricular surface leads even in the presence of predominant right ventricular hypertrophy.

A mechanical obstruction to the circulation of the blood is present in all these conditions, either within the heart or in the pulmonary circulation. This is responsible for a low fixed cardiac output that does not increase adequately on exertion. It is suggested that inadequate coronary blood flow during exercise is a result of the low cardiac output.

Cardiac pain occurring in young subjects with rheumatic or congenital heart disease suggests an obstructive lesion, and is an index of severity in those with aortic, mitral, or pulmonary stenosis.

Thanks are due to members of the visiting staff of the National Heart Hospital for allowing the author to study patients under their care, and in particular to Dr. Paul Wood, Director of the Institute of Cardology, for giving access to some of his own private material, and for advice, criticism, and encouragement.

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SIR ARTHUR KEITH

Sir Arthur Keith, who died on January 8, 1955, at the age of 88, was our oldest honorary member. His main work in cardiology was completed before the British Cardiac Society was formed. He was born in 1866 at Old Machar in Aberdeen where his father had a farm, and had nine brothers and sisters. When he was eight, the family moved to a larger farm with an attractive farm house, Kinnermit, where his brother Alec continued to farm after their father died: it remained a happy meeting place for the family for many years. Arthur does not seem to have been brilliant at school and at one time it seemed likely that he would spend his life working on the farm, but after he started as a medical student his powers developed quickly. He became an M.B. of Aberdeen in 1888, and fifty years later was rector of his old University.

Even in these early days he was keen on anatomy, but though he had qualified with distinction there was no opening for him in this line. There were not then so many hospital and school appointments and competition for the higher ones took a different form. Arthur Keith went into general practice and then went to Siam as medical officer of a gold mine, so that he could save some money to return to anatomy. Even so he had to wait and work two years in London before finding an appointment.

While in Siam he studied the anatomy of the Catarrhine monkeys, and after his return published in 1896 *An Introduction to the Study of Anthropoid Apes*. In the same year he was appointed demonstrator of anatomy at the London Hospital, at a salary of £75, but other positions such as curator of the museum soon brought this up to £300 a year.

Just before Christmas, 1899, he married Celia Gray, the daughter of an artist. This proved to be a happy companionship for nearly 35 years; unfortunately they had no children.

Throughout his life he was a keen member of scientific societies and was soon acting as secretary of the Anatomical Society. Most of his work at this stage was published in their Proceedings in the *Journal of Anatomy and Physiology* (now the *Journal of Anatomy*). Those of most interest to cardiology dealt with his studies of the auricular muscle (1902–1904), his verification of Tawara's work on the conducting system of the heart (*Lancet*, 1906, **2**, 359), and his discovery with Martin Flack of the sinu-auricular node (*J. Anat. and Physiol.*, 1907, **41**, 172).

Arthur Keith had a great facility for making friends with those who shared his interests and James Mackenzie was included amongst these. Since 1904 he had been examining many of the hearts in which Mackenzie had been interested in life and had found in sections that traversed the sulcus terminalis, where the superior vena cava entered the right auricle, a localized density of tissue in which nerve fibres seemed to terminate. When, in 1942, this journal published a paper on *The Conducting System of the Vertebrate Heart* by Francis Davies, Keith added a retrospect of his discovery (*Brit. Heart J.*, 1942, **4**, 77) in which, with characteristic generosity, he attributed the major part in this to the work that Flack was doing with him in 1906 on the hearts of moles. This series of discoveries that had started with the finding of the A-V bundle by Stanley Kent and by His in 1893 led quickly to modern views of the origin of the impulse of the heart beat and its conduction and, though details have been added since, they have not changed fundamentally.

During this period at the London, Keith made his reputation as a great lecturer and as a practical teacher with a capacity for bringing anatomy to life. It is strange reading his autobiography to find how little confidence he had in himself as a lecturer, for there were other directions in which he was not unduly modest. He was anxious to make his teaching of real use to future doctors and as well as emphasizing the relationship of the formal anatomy of any structure to its embryology and historical development, he tried to explain its functional use and the disorders to which it was liable in clinical medicine. At this time he published *Human Embryology and Morphology*, a book that has been a standby for many generations.

Sir John Parkinson adds these personal recollections. " It was my good fortune to be a pupil of Arthur Keith, the senior demonstrator of anatomy, when I was a medical student at the London Hospital, and he was a great favourite with everyone there. As a teacher he was persuasive rather than didactic, and his contact with us was personal, indeed, fatherly. He won you to learning anatomy in that he never seemed to deal out information but rather to accompany you in the search for an understanding of it.

" Keith was closely associated with James Mackenzie, then of Burnley, with whom he corresponded over many years; and they became firm friends. It was largely due to his influence and advocacy that Mackenzie was invited to join the staff of the London Hospital after he settled in London. Each had enormous respect for the other and, as so often, this ripened into lively affection. Mackenzie is quoted as saying ' Whenever Keith looks at anything, he sees something nobody else had noticed; and whenever he sees it, he begins to wonder why.'

" In those days Keith was tall and thin with sharp features, deep-set engaging eyes, and a powerful forehead. His appearance was attractive and distinguished, and his manner invariably friendly. Everyone was captivated by the softness of his voice and his modest almost diffident demeanour. There was gentleness but no lack of confidence and power in all he said and did. No one found anything but a depth of sincerity and kindliness when they knew him, and so he acquired and kept for years a wide circle of friends who became attached with affection to this great and gracious scientist."

In 1908 Keith left the London to become Curator of the Museum of the Royal College of Surgeons. His embryological researches led him to the view that the bulbus cordis did not disappear entirely but was incorporated in the outflow tract of the right ventricle. In 1909 he published a valuable series of papers on malformations of the heart showing how important this factor was in the development of pulmonary stenosis, whether valvular or infundibular. He concluded that a large number of deformed hearts are the result " of an arrest in that process which ends in incorporation of the bulbus in the right ventricle " (*Lancet*, 1909, **2**, pp. 359, 433, and 519).

In 1913 he was made a Fellow of the Royal Society and in 1921 he was knighted. He remained as curator of the R.C.S. museum for 25 years, making it one of the greatest collections in the world. It was a terrible loss when it was destroyed by bombing in May, 1941.

Before this he had reached the normal retiring age but when this time came in 1932 he was appointed by the R.C.S., Master of Buckston Browne Research Farm at Downe, in Kent. Six years before, when President of the British Association, he had appealed for the preservation of Down House as a memorial to Darwin who had lived there for forty years. Here he was to live for another twenty years and he greatly enjoyed the contacts this gave him with the younger surgeons who were working there. His own interests had become increasingly anthropological and he wrote several books, *Ancient Types of Man*, *The Religion of a Darwinist*, and *Concerning Man's Origin* and, since the war, *An Autobiography* (Watts and Co., London, 1950). His later writings were extensions and developments of his earlier work which, as he wrote himself, was mostly done before he was 45 years old.

He took part in the investigation of the Piltdown skull and so was involved in later controversies about it. He found it difficult to reconcile the human skull with the ape-like jaw but could not suspect the honesty of a fellow worker and so, with the other experts of the day, lent the weight of his judgement to the authenticity of this find: and shortly before his death when the fraud was discovered, he still found it difficult to think hardly of the original finder.

It was during the war, in his later days at Downe that the writer came to know him. In spite of his age, he made a deep impression as a man and as a mind. He was still a fine figure, with a handsome and incisive face and was still active physically and intellectually, as shown by the writing that he continued almost till the end. The writer did not know him well and believes that he had sometimes been a figure of controversy in the past, but his decisive views, with his gentle voice and the quiet way of expression that made a deep impression of strength and inward serenity were the expression of a man who knew the path that he wished to follow.

A hundred years ago it was not uncommon for a scientist to reach distinction in many branches, but this is now rare. Sir Arthur Keith covered a wide field though most of it converged on a common interest. He was distinguished as a man and as a teacher and for his work in embryology, in anatomy and functional anatomy, and in anthropology, as well as for his contributions to the theory of evolution.

MAURICE CAMPBELL

CASE REPORTS

TRAUMATIC AORTO-PULMONARY FISTULA

BY

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Aorto-pulmonary fistulæ other than patent ductus arteriosus are classified as (*a*) *congenital*, the defect being in the aortic septum and (*b*) *acquired*, implying pre-existing disease, usually of the aorta. The genesis, natural history, and symptomatology of these lesions are described and the previously recorded cases reviewed by Morgan Jones and Langley (1949), Dadds and Hoyle (1949), and Gasul *et al.* (1951).

The object of this paper is to describe a case of aorto-pulmonary fistula in a previously intact circulation caused by a needle which had presumably penetrated the chest wall.

Case Report

A male African child, aged 12, was brought to Baragwanath Hospital, Johannesburg, by his mother on 22/3/49. His only complaint was of substernal pain, reputedly occurring for the first time in recent weeks. Its site was indicated unhesitatingly as mid-line, just below the manubrio-sternal junction. The pain was described as constant, unaffected by effort, and not sufficiently severe to prevent sleep. The mother stated that the child, although active, was less so than previously. He had had, she said, no illness in the past.

The boy weighed 24 kg.; his height was 1·25 m. He was a bright, intelligent, quiet child, in no sense distressed. He had no congenital deformity. He was afebrile and not cyanosed; his fingers were not clubbed. Neck veins were not engorged but carotid pulsation was vigorous. He had no œdema. All palpable arterial pulses were bounding; pistol shot sounds were audible over the brachial, femoral, and carotid arteries. The heart rate was 100, the rhythm regular. Brachial blood pressure was 110/50, popliteal 130/60. The chest was symmetrical. There was a hyperactive left ventricular impulse. A vibrant thrill, palpable over the entire præcordium, was maximal over that part of the sternum and adjacent intercostal spaces (on both sides) between the levels of the third and fifth costal cartilages. A continuous murmur, audible over the whole chest wall, was loudest where the thrill was most intense. Both thrill and murmur had the semblance of being superficial and were accentuated in diastole. Over the third right costo-sternal junction, *where there was a scar* 1 *mm. in diameter*, the Gibson murmur had a rougher and more rasping quality than elsewhere. Exclusively over the scar just referred to the thrill was particularly intense, the sensation transmitted to the palpating finger being reminiscent of that created by a dentist's drill.

The hæmoglobin value was 12·5 g. per 100 ml., the leucocyte count 9000 with differential figures in the accepted normal range. Clinical examination was otherwise negative. Serial blood cultures were sterile. The cardiographic pattern was that of right bundle branch block.

Radioscopy showed the heart to be hyperactive; its chambers were not recognizably enlarged. The pulmonary artery and its major branches were a little prominent. Their pulsation, like that of the aorta, was vigorous but there was no true hilar dance, nor was there visible pulsation beyond the hila. The vascular pattern in the lungs was dense but not strikingly so.

A linear foreign body, resembling a needle or pin, approximately 3 cm. long, was visible within the cardiovascular shadow. The blunt end was deep to the third right costo-sternal articulation; its point was backwards and to the left at an angle of approximately 30 degrees to the sagittal plane. Fixed at its parasternal (blunt) end, the object moved, pendulum-like, in a vertical plane, synchronously with cardio-aortic pulsation; its upward movement coincided with systolic distension of the great vessels, its downward with ventricular diastole. Its arc of movement was approximately 1·5 cm.

At this stage, after deliberate consideration of the anatomical position of the needle and of the possibility of its presence being coincidental with a congenital lesion, the diagnosis of traumatic aorto-pulmonary

fistula was alone acceptable. It was accordingly decided to submit the patient to thoracotomy. Both the boy and his mother were questioned but neither was able to offer any explanation of how the needle came to enter the chest.

Hæmodynamic Studies. On 11/4/49, under local anæsthesia, a No. 6 cardiac catheter was advanced, under fluoroscopic control, as far as the pulmonary artery, just proximal to the foreign body. No attempt was made to advance the catheter beyond this point. Pressure records and blood gas analysis were as listed under the first date in Table I.

TABLE I

PHYSIOLOGICAL DATA (at rest)

Date	Pressure, mm. Hg *			Oxygen consumption	Oxygen capacity
	R.V.	P.A.	F.A.	(ml. per min)	(ml. per 100 ml.)
11/4/49	18 (Mean)	25 (Mean)	—	220	16·2
9/6/52	41/12	36/16	145–150/70–75	228	17·6

	Oxygen content (ml. per litre)					Estimated pulmonary blood flow (l. per min.)	Estimated volume of aorto-pulmonary shunt (l. per min.)
	S.V.C.	R.A.	R.V.	P.A.	F.A.		
11/4/49	114	114	118	135	156	10·5	5·3
9/6/52	121	122	132	150	167	13·4	8·3

* All pressures recorded at 45 degrees inclination of trunk. Reference level 5 cm. behind sternal angle. Corresponding antero-posterior diameter of chest 15·5 cm. R.V., Right ventricle; P.A., Pulmonary artery; F.A., Femoral artery; S.V.C., Superior vena cava; R.A., Right atrium.

Thoracotomy. This was undertaken by Mr. L. Fatti, whose record of the operation was as follows. " On 7/5/49, through an anterior tranverse incision, the heart was exposed at the level of the root of the great vessels; these were pulsating vigorously. On opening the pericardium the pulmonary artery was found to be adherent to the sternum, but the adherent area was small and easily separable; a brown stain, about 1 mm. in diameter, was then seen in the front of the pulmonary artery, just above the region of the pulmonary valve, and the needle could be felt inside. It was firmly held in the wall of the pulmonary artery, projecting inwards towards the aorta and moving up with systole. Its distal portion could not be felt; it disappeared into a violent vortex where the two great vessels communicated.

" The roots of the aorta and pulmonary artery formed a common trunk and the groove between the two vessels had disappeared. The communication extended from the origin of the right pulmonary artery to the upper limit of the ventricular septum, its vertical diameter being about 3·7 cm. and its transverse diameter slightly less; the walls of this common trunk were tense and pulsated actively in ventricular systole. Apart from the attachment of the pulmonary artery to the sternum there were no adhesions.

" Attempts were made to insert a finger or an instrument in the gap between the ventricular wall and the inter-arterial channel, in the hope of clamping the latter; but no gap could be found or made, and the valves of the two vessels were felt to close just below the open communication. It was too hazardous to remove the needle as the arterial wall was so tense and active and the operation was abandoned."

Subsequent Progress. The patient was under observation until October, 1953. Because of adverse domestic circumstances he had lived in hospital much of the time. Nevertheless, although still a bright, cheerful, uncomplaining boy his condition had deteriorated. His capacity to walk was unlimited but to run 50 yards caused moderate distress. His venous pressure had risen (Table I) and his heart had enlarged (Fig. 1), while the estimated volume of blood shunted through the fistula had increased (Table I).

Summary

An account is given of a case of aorto-pulmonary fistula, caused by a needle which had penetrated the anterior chest wall. The patient was subjected to thoracotomy but the defect, which was immediately above the ventricular septum, was so large that its closure was impracticable.

FIG. 1.—Teleradiograms, dated 6/12/52, showing enlargement of heart, dominantly of the left side. The lung fields are moderately pleonæmic. In the P.A. film the needle is seen in the third right intercostal space near the sternal margin.

Reproductions of the original films do not satisfactorily reveal the needle. The heart was then not recognizably enlarged.

Physiological data pertaining to circulatory dynamics at the time when the patient was first seen and again three years later are included. These and the patient's diminished capacity for effort indicate a progressive impairment of the circulation.

I am indebted to Dr. Margaret Findlay for the X-ray films and to Mr. L. Fatti for his notes of the operation.

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COR TRILOCULARE BIATRIATUM: FINDINGS AT THORACOTOMY

BY

C. E. DREW, P. R. FLEMING, AND A. M. JOHNSON

From Westminster Hospital

Since the description by Holmes in 1823 of a case of cor triloculare biatriatum, nearly 100 cases have been recorded. Our case seemed worth publication on account of the associated anomalies and of the method used to confirm and amplify the preoperative diagnosis.

Case Report

D.G., a male infant, had cyanotic attacks from the age of two weeks. His birth weight was 6 lb. and on admission to Westminster Hospital at the age of eight months, he was permanently cyanosed, with early finger clubbing. The second and third toes of each foot were webbed. The apex beat was in the fourth left intercostal space in the anterior axillary line, the pulmonary second sound was single and there were no murmurs. The blood pressure was 70/45 mm. Chest X-ray showed enlargement of the heart to the left, a narrow vascular pedicle in the postero-anterior view, and moderate pulmonary congestion.

Angiocardiography (Fig. 1) showed the right pulmonary artery and the aorta filling early and simultaneously and no sign of a left pulmonary artery. An abnormal pulmonary vein on the right appeared to drain into the superior vena cava or azygos vein.

A provisional diagnosis of Fallot's tetralogy with atresia of the left pulmonary artery was made and thoracotomy was decided upon with a view to a systemic-pulmonary anastomosis if this were found to be feasible.

FIG. 1.—Antero-posterior angiocardiogram at 2½ sec., showing simultaneous filling of the aorta and the right pulmonary artery.

This was carried out using hypothermia. A trans-sternal incision was made, opening into both pleural cavities. The great vessels were transposed, the aorta arising anteriorly and to the right of a small pulmonary artery which ran to the left lung. No right branch could be found, but a large artery passed from the ascending aorta to the right lung, with the usual divisions of a right pulmonary artery. A vein from the right upper lobe drained into the superior vena cava, but otherwise the pulmonary veins appeared normal.

Blood oxygen saturations in the aorta (55%) and the left pulmonary artery (59%) were estimated using a Brinkman hæmoreflector and pressures in the left pulmonary artery (22/5 mm. Hg) and infundibulum (65/5 mm.) were measured in quick succession, with a Sanborn electromanometer. Pulmonary valvular stenosis was diagnosed and pulmonary valvotomy was performed. The oxygen saturations in the aorta and the left pulmonary artery were now 81 per cent and 80 per cent respectively, but the pulmonary artery and infundibular pressures were unchanged. The possibility of detaching the right pulmonary artery from the aorta and anastomosing it with the left was considered but the similarity of the oxygen saturations in the aorta and left pulmonary artery suggested a single ventricle. This was confirmed by the pressures in "right" and "left" ventricles which were both 48/0 mm. Hg, the form of the two curves being identical. No further operative procedure was possible and the chest was closed. The child died three hours later.

Autopsy

Autopsy (Fig. 2). The venæ cavæ were normal apart from the anomalous vein from the right upper lobe. There was a hypertrophied common ventricle with no trace of a septum. The abnormal arrangement of the great vessels found at operation was confirmed; there was no ductus arteriosus. The pulmonary valve was stenosed, the cusps being represented by two fleshy papillæ, the commissures between which had been split. The left atrium showed hypertrophy (3 mm.) with thickened endocardium; the inter-atrial septum was intact. The pulmonary veins were grossly hypertrophied. The mitral orifice was minute, with no cusps.

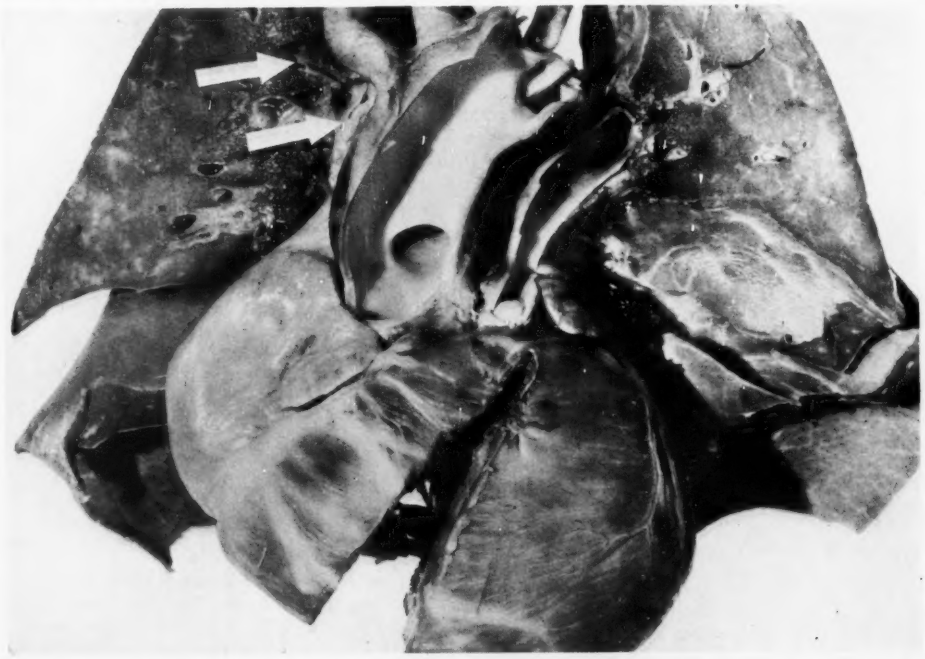

FIG. 2.—Anterior aspect of the autopsy specimen, showing the orifice of the large branch of the aorta passing to the right lung; the left pulmonary artery with valvular stenosis; the anomalous vein (upper arrow) from the right upper lobe draining into the superior vena cava (lower arrow).

Histological examination of the left atrium showed, in addition to muscular hypertrophy, gross endocardial thickening, the deeper part of which was almost wholly elastic, with a layer of muscle tissue running through it, resembling the appearances seen in fibroelastosis.

Discussion

The syndrome of single ventricle with pulmonary stenosis has recently been reviewed by Campbell *et al.* (1953) and only the features in which our case differed from the patterns they described will be discussed.

The most remarkable feature is that life was maintained at all in the presence of such severe mitral stenosis with an intact inter-atrial septum. It would seem that the pulmonary stenosis greatly reduced the blood supply to the left lung and that a large proportion of the total pulmonary venous drainage was carried by the anomalous vein from the right upper lobe. The increase in left pulmonary blood flow resulting from the valvotomy could have contributed to the child's death by precipitating pulmonary œdema.

Nadas *et al.* (1953) described three cases of Fallot's tetralogy with atresia of the left pulmonary artery. The angiocardiogram suggested this state of affairs in our case and the possibility of performing systemic-pulmonary anastomosis with a branch of the right pulmonary artery was considered, to avoid clamping its main trunk. There was, in fact, no trace of a right pulmonary artery, the right lung being supplied by the large vessel from the ascending aorta.

This method of diagnosis by means of pressure measurements and estimations of oxygen saturations after transverse thoracotomy has not been widely reported. In those cases in which certain preoperative diagnosis is not possible, its use seems worth while as the combined anatomical and physiological study may provide the additional information needed for exact diagnosis. This case illustrates the importance of recording pressures from all the cardiac chambers as unsuspected lesions may otherwise be missed.

Summary

A description is given of a fatal case of cor triloculare biatriatum in which the following associated anomalies occurred: (1) pulmonary valvular stenosis; (2) absence of the right pulmonary artery, the right lung being supplied by a large branch of the ascending aorta; (3) congenital mitral stenosis, with intact inter-atrial septum and endocardial fibroelastosis of the left atrium; and (4) anomalous right pulmonary venous drainage.

These anomalies are discussed and an account is given of the diagnostic use of pressure measurements and estimations of oxygen saturation at operation. A technically successful pulmonary valvotomy may have contributed to the fatal issue.

We wish to thank Dr. A. A. Cunningham of Kingston Hospital who referred the case, Dr. C. J. Gavey for his advice and encouragement in the preparation of this paper, Dr. A. D. Morgan for the autopsy report and Dr. Peter Hansell for the photographs

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ABSTRACTS OF CARDIOLOGY

Edited in collaboration with Abstracts of World Medicine

Use of " Dibenzyline " as a Vasodilator in Patients with Severe Digital Ischæmia. D. G. FRIEND and E. A. EDWARDS. *Arch. intern. Med.*, **93**, 928–937, June, 1954.

" Dibenzyline " (N-phenoxy*iso*propyl-N-benzyl-β-chloroethylamine hydrochloride) is one of a series of compounds related to " dibenamine " (N:N-dibenzyl-β-chloroethylamine) whose chief characteristic is their ability to block adrenergic impulses. It is active on both intravenous and oral administration and exerts a striking effect on the peripheral vessels. In normotensive and hypertensive subjects the peripheral blod flow has been found to increase by as much as 500% after intravenous injection of the drug, but in patients with peripheral arterial disease there was much less increase in blood flow. Central effects are less marked than those at the periphery. The vasodilatation results in hypotension, the blood pressure falling by 15 to 20 mm. Hg.

The present authors have given dibenzylene to 23 patients with digital ischæmia, 14 of them having true Raynaud's disease and 9 ischæmic changes due to other diseases. The drug was given in capsules by mouth four times daily, the total daily dosage varying from 20 to 80 mg.

Marked benefit resulted in patients whose symptons were chiefly due to vasospasm. All the patients with true Raynaud's disease experienced a warmth of the hands and feet, with loss of the paroxysms of vasospasm and relief from pain due to ulceration of the finger-tips. Similar relief was obtained in a case of scleroderma in which there were changes in the fine peripheral vessels. Inconsistent results were observed in cases where organic vascular occlusion was predominant.

The authors consider that dibenzylene is the most effective vasodilator drug currently available. They are of the opinion that it will give better results than sympathectomy in most cases of ischæmia of the fingers, but that it may not prove so effective for ischæmia of the toes. This is partly because organic occlusion occurs more frequently in the vessels of the legs and partly because lumbar sympathectomy is technically a satisfactory procedure. *J. Lister*

The Relation between Tuberculosis and Congenital Heart Disease, with Special Reference to Pulmonary Stenosis. G. FEGIZ and M. MANCUSO. *Arch. Chir. Torace*, **11**, 401–425, July–Sept., 1954.

It was for long thought that pulmonary tuberculosis and congenital heart disease, especially in its cyanotic forms, were incompatible. This was probably because many seriously affected patients died of the heart disease and mild cases went unrecognized. In fact the association has been reported for almost all types of congenital cardiac lesion, and the incidence is particularly high in pulmonary stenosis.

The authors here present, from the Institute of Surgical Pathology, University of Rome, 3 cases of tuberculosis among 28 patients with pulmonary stenosis, representing an incidence of over 10%, as compared with only one case of tuberculosis among 110 patients with Fallot's tetralogy. The poor pulmonary blood circulation, resulting in an inadequate supply of antibodies and lymph, is thought to predispose to infection, just as the opposite state of affairs which exists in mitral stenosis is thought to protect the lungs. In the 3 cases described pulmonary valvotomy was performed, with subsequent improvement in the tuberculous condition. The first patient had no other treatment, and follow-up examination for over 3 years showed rapid and complete healing; the other 2 patients received streptomycin. Single examples of the association of tuberculosis with tricuspid atresia, the Eisenmenger complex, and transposition of the heart are recorded. No case could be found of associated tuberculosis in patients with atrial septal defect or patent ductus arteriosus. *A. Paton*

Atrial Septal Defect. Clinical and Physiologic Response to Complete Closure in Five Patients. S. G. BLOUNT, H. SWAN, G. GENSINI, and M. C. MCCORD. *Circulation (N.Y.)*, **9**, 801–812, June, 1954.

Direct closure of an uncomplicated atrial septal defect was performed under hypothermia on 5 patients aged 4 to 26 years, with good results in all cases. Cooling to 25° to 30° C. was effected by immersion in ice water under anæsthesia. Operation was by the method of Lewis and Taufic (*Surgery*, 1953, **3**, 52; *Abstracts of World Medicine*, 1953, **14**, 124) in which an anterior, transverse, bilateral thoracotomy with splitting of the sternum gives access to the right atrium, which is opened under direct vision with occlusion of cardiac inflow for a period not exceeding 10 minutes. The defect was closed with silk sutures, strict measures being taken to prevent coronary arterial air embolism.

The physiological investigations carried out and the selection of suitable cases are discussed in detail. Patients with a large shunt but without gross pulmonary hypertension are the most suitable, and 4 out of the 5 cases operated upon were of this type.

Postoperative investigation of the patients showed that the defect had been completely closed in all cases, but

the pulmonary arterial pressure was slightly raised in 2 patients, probably owing to structural changes in the pulmonary capillary bed. *S. F. Stephenson*

Results of Pulmonary Valvotomy and Infundibular Resection in 100 Cases of Fallot's Tetralogy. M. CAMPBELL, D. C. DEUCHAR, and R. BROCK. *Brit. med. J.*, **2**, 111–122, July 17, 1954.

In a previous paper (Campbell and Deuchar, *Brit. med. J.*, 1953, **1**, 349; *Abstracts of World Medicine*, 1953, **14**, 215) the results of treatment by the anastomotic or indirect type of operation introduced by Blalock in 200 cases of congenital pulmonary stenosis were reported, including 165 cases of Fallot's tetralogy. The authors now report the results in a parallel series of 100 cases of Fallot's tetralogy in which a direct attack was made on the stenosis, and pulmonary valvotomy or infundibular resection, or both, was carried out at Guy's and the Brompton Hospitals, London, and discuss in some detail the 61 cases operated on before the end of 1952. Of these 61 patients, 23 underwent valvotomy, 25 infundibular resection, and 13 the combined operation, and a " very good " or " good " result was obtained in 39 (64%), compared with 77% of the series treated by the Blalock type of operation. The operative mortality in these early cases was 18% compared with 8·5% for the anastomotic procedure, but for the whole series of 100 the mortality fell to 15%.

The technical details are not discussed, but it is emphasized that the direct operation is not a " blind " one, since the exact position and degree of the stenosis can be accurately assessed by external examination and the diagnosis verified by means of direct pressure readings and, if necessary, by introduction of a finger into the right ventricle. It is also stressed that the operation on the stenosis itself should be persisted with until satisfactory pressure records are obtained, which may involve 10 or 12 instrumental entries into the heart.

After operation a reduction in cyanosis was noted which was proportionate to the increase in exercise tolerance, but the maximum clinical improvement was sometimes delayed for a period of months. The average hæmoglobin level fell from 130 to 103%, and the cardiothoracic ratio increased by 4 to 5 points, these being similar to the findings after anastomotic operations. The electrocardiographic changes following the direct operation are discussed in detail. Postoperative cardiac catheterization showed widely varying pressure changes; in general, however, the removal of stenosis led to an increase in pulmonary flow from preoperative values ranging from 40 to 55% of the systemic flow to values ranging from 75 to 150%. Arterial oxygen saturation rose from 75 or 80% to 90 or 95% in some cases.

The danger of over-correction of the right-to-left shunt and production of a condition like Eisenmenger's complex by opening up the pulmonary stenosis too freely is a theoretical criticism of the direct operation, but there is no evidence that this ever occurs in practice, since the stenosis cannot be so completely removed so as to allow the pulmonary circulation to bear the full brunt of the right ventricular thrust.

[This article, taken in conjunction with its predecessor, affords a most valuable and important contribution to the study of the results of surgical treatment of pulmonary stenosis. In Fallot's tetralogy there would appear to be little difference between the results of the indirect and direct operations. But if in the future hypothermia and other developments will permit opening of the heart to relieve the stenosis and at the same time to close the interventricular septum the advantages will all be on the side of the direct operation.] *T. Holmes Sellors*

The Long-term Prognosis of Cardiac Infarction. G. I. SHMAL'TS. *Klin. Med.* (*Mosk.*), **32**, 58–67, May, 1954.

The end-results of cardiac infarction have become much better in recent years than formerly.

The author has studied 180 patients in various stages of cardiac infarction; these he defines as: (1) the stage of shock, lasting 2 or 3 days; (2) the stage of consolidation, lasting from the 4th to the 15th day; and (3) the stage of myocardial sclerosis. Of these 180 patients, 2 died in the first stage, and 23 in the second and third stages (but 2 of these from causes other than the results of infarction); 12 of the 23 died from cardiovascular failure (7 after a second infarction), 8 in an anginal attack, and one from spread of thrombosis along the branches of the coronary arteries. Of the 7 patients suffering a second infarction, 4 died in less than one year, one lived a year after the second attack, one survived for 2 years, and one for 4 years.

Age is an important factor, for whereas 4 out of 43 patients aged between 41 and 50 died (9·3%), 17 of 101 aged between 51 and 70 died. Sex appears to have little effect, the reported higher mortality in women being due to the later average age of onset. The prognosis is worse with infarcts of the anterior wall than those of the posterior wall, and still worse if both are involved. The presence of hypertension before infarction is of bad prognostic significance, since although there was no marked difference in the percentage of deaths during the 3 years of this investigation between those with and those without hypertension, yet amongst those surviving infarction 3 years or more the proportion with a history of hypertension was notably lower than in a group with a shorter interval between their infarction and the date of review, suggesting that patients with hypertension tend to die earlier than those with a normal blood pressure before infarction.

The most important factor in prognosis, in the author's opinion, is the willingness of the patient to submit to a strict regime of absolute rest in the early stages of the disease. Of the 155 surviving patients in the present series, 109 resumed their former work and 26 undertook lighter work; about half (71) of these 135, however, had to give up work at intervals owing to anginal attacks. Resumption of work should not be permitted or attempted until at least 3½ to 4 months after the attack.
L. Firman-Edwards

The Patient's Capacity for Work after Myocardial Infarction. A. T. NOVIKOV. *Klin. Med.* (*Mosk.*), **32**, 67–74, May, 1954.

The outlook for patients with myocardial infarction has much improved in recent years. In the present communi-

cation the author reviews 171 cases treated between 1945 and 1952 (including 12 patients treated before 1945 who were re-admitted with a second infarct or for symptoms of chronic coronary insufficiency). The patients, who were all men engaged in intellectual work and subjected to frequent mental strain, were divided into three groups: (1) 107 whose illness had been followed over a number of years; (2) 29 whose capacity for work was assessed only on discharge from hospital and who had since left for other districts; and (3) 35 who died during the period under review.

Of those in Group 1, 87 were found capable of work for varying periods, this figure representing 51 per cent of the total number of patients, and 81 per cent of the group. As to age, 9 of them were between 36 and 40, 48 between 41 and 50, 29 between 51 and 60, and one was over 60. Full office hours of work were resumed by 69 of them, while only 18 had to have their working hours curtailed; but 32 of the full-time workers had eventually to give up work, as had 3 of the short-time workers.

Of the patients in Group 2, 15 were found to be capable of work, and 14 incapable. The latter included 8 with septal infarcts which involved also the anterior or antero-lateral wall, while the remaining 6 had infarction of the anterior, posterior, or antero-lateral walls without septal involvement; 11 of these patients had had anginal attacks before their infarction for periods varying from 2 to 9 years. Among the 15 found capable of work there were none with infarcts involving the septum.

Of the 35 patients in Group 3, 13 died after the first infarct, 21 after a second infarct, and one after a third. In 13 cases death occurred in the first 3 days of the illness, in 7 between the 8th and 13th days, in 11 after 4 to 12 months, and in 4 cases after 2 to 3 years.

The author concludes that the prospect of returning to work is poor (1) in cases with a history of frequent anginal attacks before the infarction; (2) in those with frequent anginal attacks after the infarct or with evidence of cardiovascular insufficiency; and (3) in those with septal involvement. Strangely enough, ventricular aneurysm is, in his experience, not necessarily a contra-indication to resumption of work. In those with limited capacity, the working time should not exceed 6 hours per day. *L. Firman-Edwards*

Circulatory Changes in Acute Myocardial Infarction. R. P. GILBERT, M. GOLDBERG, and J. GRIFFIN. *Circulation (N.Y.)* **9**, 847–852, June, 1954.

At Cook County Hospital, Chicago, the cardiac output was determined with Evans blue by the method of Hamilton in 20 subjects soon after acute myocardial infarction. The arterial and venous blood pressure, arm-to-tongue circulation time, plasma volume, and hæmatocrit were also determined. Of the 20 patients, 13 showed signs of congestive heart failure and severe shock. The average cardiac output in the whole series was 3·3 litres per minute (S.D. 1·6) and the circulation time 32 seconds (S.D. 16). In individual patients the degrees of reduction of cardiac output and prolongation of the circulation time compared with normal values were roughly proportional to the clinical severity of the attack. Vasoconstriction, tending to sustain the blood pressure, was evidenced by an increased peripheral resistance. No major changes in plasma volume were found even when shock was sustained. The authors suggest that the aim in treating patients with heart failure and sustained shock following acute myocardial infarction should be to increase the cardiac output. In this connexion the recent work on pressor amines and intra-arterial infusions is of considerable interest and it is hoped that more experimental work will be done in this field.

A. I. Suchett-Kaye

Acute Myocardial Infarction Treated by the Chair Rest Regimen. Thirty Consecutive Cases Managed by the Levine Armchair Method. J. L. WILSON and J. H. WARD. *J. Amer. med. Ass.*, **155**, 226–230, May 15, 1954. 18 refs.

The authors report the results obtained with a chair-rest regimen in the management of 30 consecutive proved cases of myocardial infarction at the United States Naval Hospital, Bremerton, Washington. The patient was lifted into a large, comfortable, upholstered chair by the bedside as soon as shock had passed and the presence of complications had been excluded. The majority of the patients tolerated 3 to 6 hours in the chair on the first day and at least 10 hours on the third or fourth day. Other treatment included administration of anti-coagulants, support for the lower limbs by application of an elastic bandage or, preferably, elastic stockings, and administration of oxygen, liberally in the first 48 hours and then as a routine for one hour after each meal during the first week. At night the head of the bed was raised to avoid hypostatic congestion of the lungs. The patient was assisted to a bedside commode, thus avoiding the exertion necessary in using a bed-pan. After 21 days walking was allowed, activity being gradually increased during the next 14 days. On the average the patient was up in a chair on the 5th day, seated all day by the 8th day, ambulant by the 24th, and discharged on the 33rd day.

Of the 30 patients, 3 died—one from massive infarction involving the posterior and lateral aspects of the heart, one from rupture of the left ventricle, and one from perforated peptic ulcer and peritonitis in addition to acute myocardial infarction. *H. G. Farquhar*

Long term Anticoagulant Therapy. Further Experiences. J. TULLOCH and I. S. WRIGHT. *Circulation (N.Y.)* **9**, 823–834, June, 1954.

As a contribution to the study of the problems of the long-term prophylactic and therapeutic use of anti-coagulant therapy in thrombo-embolic conditions, a detailed analysis of 227 cases treated in out-patients at the New York Hospital and in private practice with dicoumarol or tromexan (ethyl biscoumacetate) for 4 weeks or longer is presented. Some of the patients had been taking anticoagulants for as long as 8 years. The conditions treated were mainly rheumatic heart disease with peripheral and pulmonary embolism, thrombophlebitis, myocardial infarction, and myocardial ischæmia. A total of 546 thrombo-embolic episodes had occurred before treatment with anticoagulant drugs, recurrent thrombophlebitis with pulmonary embolism

alone accounting for nearly two-thirds of these, and in all cases the aim of long-term anticoagulant treatment was to prevent the occurrence of further episodes.

At the start of treatment the prothrombin time was estimated 2 or 3 times weekly, later only once weekly, and after a few months once every 10 to 14 days or at longer intervals. A prothrombin time of 25 to 30 seconds (normal control times 14 to 16 seconds) was aimed at, hæmorrhagic complications being liable to occur with a prothrombin time of 40 seconds or over: 43 patients (18·9%) suffered such complications on 70 occasions. Treatment was not stopped when the bleeding was not severe—for example, subcutaneous ecchymosis or slight bleeding from the gums or from hæmorrhoids—and the prothrombin time relatively low, but 11 patients had to be given vitamin K or K_1 and two of these also received fresh blood; one patient died from cerebral hæmorrhage. On the other hand, in 33 subjects (14·5%) the prothrombin time was well over 40 seconds on 51 occasions without the occurrence of bleeding.

The authors realize that continued treatment with anticoagulants does not give complete protection from thrombo-embolic incidents, even when the prothrombin time is markedly prolonged—indeed, 26 patients (11·4%) experienced a total of 40 definite or possible thrombo-embolic episodes during treatment. They conclude, however, that "properly controlled out-patient anticoagulant therapy is relatively safe and will lessen the incidence of thrombo-embolic episodes in patients previously suffering from such complications".

A. I. Suchett-Kaye

Treatment of Venous Thrombosis with Anticoagulants. Review of 1135 Cases. J. MARKS, B. M. TRUSCOTT, and J. F. R. WITHYCOMBE. *Lancet*, **2**, 787–791, Oct. 16, 1954.

In the Cambridge area during the past 5 years 1,135 patients with superficial and deep peripheral venous thrombosis have been treated with anticoagulant drugs. The regimen used was the administration, as soon as the diagnosis was made, of ethyl biscoumacetate, 1·2 g., or phenylindanedione, 250 mg. by mouth, and the intramuscular injection of heparin, 150 mg., with hyaluronidase, 0·1 mg. This was followed by heparin in a dose of 50 mg. combined with 0·1 mg. hyaluronidase 4-hourly for four doses only. Subsequent dosage with phenylindanedione or ethyl biscoumacetate was regulated by the trend in the level of the prothrombin time as estimated by a modified Quick one-stage technique. Bed rest and splinting were advised for patients with pain, but active exercises in bed were encouraged as soon as pain subsided. On the average, patients attained freedom from pain in 18 hours in cases of superficial venous thrombosis and in 3 to 4 days in those of deep thrombosis, while the average stay in bed was 3 to 5 days in the former and 5 to 7 days in the latter. Hæmorrhagic incidents were rare, and it was possible to treat 307 of the patients in their own homes without the occurrence of untoward side-reactions. Three patients died while undergoing anticoagulant therapy, all from pulmonary embolism. In the 5-year period of the study, despite vigilance in the early diagnosis and treatment of venous thrombosis in the leg, 54 cases of sudden, unheralded, fatal pulmonary embolism occurred among patients who were not receiving anticoagulants.

The authors conclude that the morbidity and mortality of peripheral venous thrombosis can be materially reduced by anticoagulant therapy, but the incidence of fatal, unheralded pulmonary embolism remains uninfluenced.

Bernard Isaacs

Renal Hæmodynamics in Valvular Heart Disease. J. HIMBERT, A. THÉARD, P. GELÉ, L. SCÉBAT, and J. LENÉGRE. *Arch. Mal. Cœur*, **47**, 747–766, Sept., 1954.

Measurements of the renal plasma flow (R.P.F.) by determining PAH clearance, and of the glomerular filtration rate (G.F.R.) by determining mannitol clearance, were made on 60 patients with varying degrees of disability caused by valvular heart disease. None had evidence of renal disease, and few were over 50 years of age. They were classified in five groups: (I) with normal heart or with lesions causing no disability; (II) with pulmonary congestion due to mitral stenosis, but without heart failure; (III) recovering from congestive heart failure; (IV) in congestive heart failure without œdema; and (V) in congestive failure with œdema.

There was a progressive diminution in the average R.P.F. from Group I to Group V, with some overlapping of the individual values between groups: in all cases in Group V, however, the values were well below the lowest limit of normal. A similar diminution in the average G.F.R. was noted, but this fell to a smaller degree than the R.P.F., so that the filtration fraction rose progressively from Group I to Group V. In Group V, the only group with œdema, the G.F.R. was not significantly lower than in Group IV. No clear relationship between the G.F.R. and the presence of œdema was found, for in 2 out of the 9 patients with œdema the G.F.R. was virtually normal, whereas in some patients in Group III who had recovered from failure with œdema the G.F.R. was still significantly reduced.

J. A. Cosh

Calcification of the Mitral Valve Annulus and Its Relation to Functional Valvular Disturbance. M. A. SIMON and S. F. LIU. *Amer. Heart J.*, **48**, 497–505, Oct., 1954.

Calcification of the mitral valve annulus is not infrequent. Its incidence was 10 per cent in 590 unselected, consecutive autopsies on subjects of all ages. The incidence was higher in individuals over 50 years of age.

While calcification of the annulus of the mitral valve may occur in rheumatic heart disease, it is primarily a degenerative process similar, in many respects, to arteriosclerosis. In the majority of cases the process does not affect the mitral valve leaflets. Variable degrees of calcification of the aortic valve, presumably on a non-rheumatic basis, were associated in approximately 25 per cent of the subjects whose hearts showed calcification of the mitral valve annulus.

In a selected series of 24 cases of mitral annulus calcification, apical systolic murmurs presumably referable to the mitral valve, were heard in 15 cases. In 9 of

these 15 cases the quality of the murmurs was such (loud, rough, or musical) as may be associated with functional derangement at the mitral orifice, and in 5 instances a clinical diagnosis of mitral regurgitation was made.

Extensive calcification of the mitral valve annulus which may produce variable degrees of mitral regurgitation can be strongly suspected in individuals over 50 years of age having loud, rough, or musical systolic apical murmurs who give no history of previous rheumatic heart disease.—[From the authors' summary.]

Biopsies of the Lung and Atrial Appendages in Mitral Stenosis: Correlation of Data from Cardiac Catheterization with Pulmonary Vascular Lesions. J. DENST, A. EDWARDS, K. T. NEUBUERGER, and S. G. BLOUNT. *Amer. Heart J.*, **48**, 506–520, Oct., 1954.

Lung biopsies from 23 patients with mitral stenosis who were studied by cardiac catheterization prior to mitral commissurotomy were examined histologically. In the majority of cases the muscular arteries and arterioles exhibited prominent fibroelastic intimal thickening, and in 32 per cent the media appeared hypertrophic. In general, a positive correlation existed between the degree of vascular alteration and the pulmonary arteriolar resisance and mean pulmonary arterial pressure in the more severe cases of pulmonary hypertension. The hæmodynamic pattern varied considerably in patients who exhibited less severe vascular lesions. A functional component was believed to be of as great importance in the development and maintenance of pulmonary hypertension as the organic vascular changes. It was considered that surgery should not be denied the patient either on the basis of data obtained by cardiac catheterization or because of the pulmonary vascular lesions, which are not usually severely obstructive although almost always present.

The histologic findings in 75 resected atrial appendages were reviewed; the results were in general agreement with those of other recent investigations.—[Authors' summary.]

Experiences in the Surgical Treatment of Aortic Stenosis. W. H. MULLER, A. A. KATTUS, J. F. DAMMANN, and R. T. SMITH. *J. thorac. Surg.*, **28**, 516–535, Nov., 1954.

The authors give a brief history of the surgical treatment of aortic stenosis, and present the results in 25 of their cases subjected to aortic valvotomy by the transventricular route.

Of their 25 patients, one group of 16 had "pure" aortic disease; calcification of the valve was present in 13 of these cases and also in 8 out of the 9 in the second group, in which associated mitral disease was present. The patients' ages ranged from 14 to 63 years. There were 4 operative deaths, 2 in each group. The authors stress the difficulty of objective postoperative assessment, but from the patients' statements conclude that the results in the cases of isolated aortic disease were better than in those with associated mitral valve lesion. The authors conclude that the early results are encouraging.

J. R. Belcher

Antibiotic Therapy of Bacterial Endocarditis. VI. Subacute Enterococcal Endocarditis: Clinical, Pathologic and Therapeutic Consideration of 33 Cases. J. E. GERACI and W. J. MARTIN. *Circulation (N.Y.)*, **10**, 173–194, Aug., 1954.

During the first decade of treatment of bacterial endocarditis with antibiotics, 33 (approximately 10%) of the cases encountered at the Mayo Clinic were caused by enterococci (Lancefield's Group-D streptococci), which are highly resistant to penicillin. Endocarditis followed a urological procedure in 16 of the 33 cases, transurethral resection of the prostate accounting for 12 of these. In 15 cases there was no history of antecedent heart disease, while 2 patients had congenital, and the rest probably rheumatic, cardiac lesions. The usual clinical features were present, and major embolism occurred in 23 cases.

The organism isolated from the 31 treated patients were tested *in vitro* for sensitivity to various antibiotics, alone and in combination, by a bacteriostatic plate-dilution method, and in 5 cases the bactericidal effect of antibiotics added to active cultures was studied by means of survival counts. In each case the most effective combination was that of penicillin with dihydrostreptomycin. Of 18 patients treated with penicillin alone, only 7 were cured, whereas of 12 patients given adequate doses of penicillin and dihydrostreptomycin, the infection was controlled in 10.

[For full practical details of the recommended therapy and its bacteriological control the original paper should be consulted.] *D. Emslie-Smith*

Myocardial Toxoplasmosis. J. W. PAULLEY, R. JONES, W. P. D. GREEN, and E. P. KANE. *Lancet*, **2**, 624–626 Sept. 25, 1954.

Three cases in which myocarditis was believed to be due to toxoplasmosis were seen at the East Suffolk and Ipswich Hospital in the 12 months ending June, 1954. It is suggested that toxoplasmosis should be considered as a possible ætiological factor in any case of myocarditis of unknown ætiology. The first patient, a mentally dull man, had a pleural effusion, recurrent hemiplegia, and an enlarged heart. The patient's serum was positive for toxoplasmosis by the dye test at 1 in 64 and by the complement-fixation test at 1 in 16. There was a strong family history of mental retardation and unexplained "myocarditis". The other 2 patients had idiopathic cardiomegaly; the serum in one of these was positive for toxoplasmosis by the dye test at 1 in 32 and by the complement-fixation test at 1 in 16, and in the other at 1 in 512 and 1 in 32 respectively. A necropsy report on a sister of the first patient revealed "a non-specific myocarditis in the healing phase following severe focal necrosis". Blood culture for *Toxoplasma* was negative.

The authors believe that these were cases of chronic toxoplasmosis, probably acquired rather than congenital.

E. G. Rees

Splitting of the First and Second Heart Sounds. A. LEATHAM. *Lancet*, **2**, 607–613, Sept. 25, 1954.

An auscultatory and phonocardiographic study of the heart sounds in health and disease is presented in this

paper, which is based on experience at the London Hospital and the National Heart Hospital, London. Only those sounds which can be clearly heard are considered in detail.

Splitting of the first heart sound is found in most healthy people and is usually more easily heard during expiration. The second component of the split first sound is usually louder at the tricuspid area and occurs after the initial rise in pressure in the carotid artery. It is thought, therefore, that the first element is due to closure of the mitral valve and the second to closure of the tricuspid valve. The interval between the sounds is usually 0·02 to 0·03 second. Splitting of the first heart sound must be distinguished from the addition of an auricular sound, a presystolic murmur, and the early systolic click of a dilated pulmonary artery or ascending aorta. An added auricular sound preceding the first sound is of lower pitch, and is separated by a wider interval than is common with a split first sound. A presystolic murmur is loudest at the apex after exertion and is commonly accompanied by a loud first sound, an opening snap, and a mid-diastolic murmur. The early systolic click which sometimes accompanies dilatation of the pulmonary artery or the proximal aorta is sharp in quality and loudest at the base of the heart; it is heard at the apex only if very loud.

The second heart sound is normally split because of the slightly asynchronous contraction of the ventricles and earlier closure of the aortic valve. The interval between the two components is wider in inspiration (0·05 second) and may not be detectable in expiration. The gap between the aortic and pulmonary components of the second heart sound is unduly wide in the presence of pulmonary stenosis and of conduction delay due to right bundle-branch block. This wide splitting is best appreciated in expiration, during which the interval is normally very small or undetectable. A combination of an early pulmonary systolic sound and a widely split second sound suggests the presence of pulmonary stenosis; but wide splitting may also be due to early closure of the aortic valve in mitral incompetence. Conduction delay in left bundle-branch block may cause wide splitting due to very late closure of the aortic valve. This state of affairs can be recognized by the fact that the gap diminishes in inspiration when pulmonary valve closure is delayed. In pulmonary hypertension the second heart sound at the pulmonary area is loud, but splitting may be absent or the gap extremely small.

The third heart sound can usually be distinguished from the pulmonary component of a split second sound by its quality, site of maximum intensity, and behaviour during respiration. Its differentiation from an opening snap is important, because of its completely different significance; in mitral valvular disease it indicates incompetence rather than stenosis.

[This paper is very concise and well illustrated and should be consulted in the original.] *D. W. Barritt*

Cardiac Involvement in Hemochromatosis. H. P. Lewis. *Amer. J. med. Sci.*, **227**, 544–558, May, 1954.

Hæmochromatosis is a rare disease and its presence is often only recognized at necropsy. Its manifestations are varied: it may occur without causing pigmentation or diabetes, and it may present primarily as a cardiac disease; it is this aspect of the condition which is discussed in this paper from the University of Oregon Medical School.

The excessive storage of iron which occurs in hæmochromatosis may come about in three ways: it may be (1) endogenous, from increased absorption of iron; (2) exogenous, excess iron entering the body by way of multiple blood transfusions; or (3) due to nutritional disturbances, such as pellagra, which cause increased accumulation of iron in the tissues. The author describes 2 cases which illustrate the endogenous and exogenous mechanisms respectively.

Discussing the effect on the heart the author suggests that biochemical changes in enzyme systems and the destruction of phosphate-containing protein substances in the nuclei and sarcoplasm of cardiac muscle by the excess iron may be the cause of myocardial failure rather than any actual injury caused to the cardiac muscle cells by deposits of hæmosiderin. Cases of myocardial hæmosiderosis are extremely refractory to the ordinary treatment usually employed for congestive heart failure. It is suggested that repeated bleeding may remove some of the excess of iron and so prevent cardiac damage. *James W. Brown*

Atrial Septal Defects. A New Surgical Approach and Diagnostical Aspects. [In English]. V. O. Björk, C. Crafoord, B. Jonsson, S. R. Kjellberg, and U. Rudhe. *Acta chir. scand.*, **107**, 499–515, July 6, 1954.

Before surgical treatment of an atrial septal defect can be undertaken, catheterization of the heart is always necessary in order to verify the diagnosis, to calculate the size of the shunt, and to measure the pulmonary arterial pressure. It is noted, however, that where the defect is close to the valvular plane the main stream of blood is directed towards the tricuspid orifice and is expelled directly into the right ventricle with negligible mixing in the right atrium, so that a ventricular septal defect may be wrongly suggested by the results of blood gas analysis. The authors, working at the Karolinska Institute and Hospital, Stockholm, have found the usual methods of angiocardiography unsatisfactory for the adequate radiological diagnosis of atrial septal defects and have therefore devised a new technique whereby the contrast medium is injected into the left atrium by means of a catheter passed through the defect via the saphenous vein. In addition, an inflatable balloon fixed to the catheter and filled with contrast medium is used to outline the defect and indicate its size. With this technique it is possible to demonstrate or exclude a complicating mitral stenosis, but a co-existing abnormal venous return cannot be excluded.

A new method is described for the closure of an atrial septal defect which is a modification of the operation devised by Sondergaard and Husfeldt. A groove is then dissected between the atria from a point between the superior vena cava and the right superior pulmonary vein down to the inferior vena cava, continuing until the muscle bundles are seen crossing from one atrium to the other. Guided by a finger introduced through the right

auricular appendage, a curved needle is then introduced at the root of the aorta 1 to 2 cm. behind the origin of the right coronary artery, passed subendocardially behind the defect until the valvular plane is reached, rotated forwards to avoid the coronary sinus, and brought out behind the inferior vena cava. The needle is brought out through the left atrial wall as close to the atrio-ventricular border as possible. The heavy (No. 4 or 5) silk thread which has been passed with the needle is then tied over a piece of fascia or muscle in the dissected groove between the cavæ and the right pulmonary veins and drawn tight until the palpating finger finds the defect completely closed.

Of the 12 patients so treated, 10 have survived the operation and the immediate results seem satisfactory, although it is too soon yet to assess the end results, the longest follow-up being 7 months. The article is fully illustrated, and detailed descriptions are given of 4 of the cases treated. *F. J. Sambrook-Gowar*

Repair of Atrial Septal Defects in Man under Direct Vision with the Aid of Hypothermia. F. J. LEWIS, R. L. VARCO, and M. TAUFIC. *Surgery*, **36**, 538–556, Sept., 1954.

The authors discuss some of the advantages and disadvantages of hypothermia in performing intracardiac operations, and stress the simplicity of the procedure in comparison with the setting up of an artificial circulation. They remark that when possible it is obviously better to repair atrial septal defects by direct vision, and report, from the University of Minnesota Medical School, 11 cases in which they were able to do this with the aid of hypothermia. They describe their technique in detail, and stress the importance of exploring the defect completely by palpation through the auricular appendage before the auricle is opened. Cooling was achieved by means of refrigerating blankets (illustrated) containing tubes through which a solution of alcohol at 25° F. (−4° C.) was run. The defects were, when possible, repaired with interrupted sutures.

Of the 11 patients, one died during the operation and one 3 days later of complete heart block, in another case the operation had to be abandoned because of fibrillation, but in 8 cases the septal defect was successfully sutured; in 5 of these cases postoperative cardiac catheterization showed no evidence of a shunt. Ventricular fibrillation occurred in 4 of the patients, but was easily controlled on each occasion. The authors state that the greatest hazard of the operation is erroneous preoperative diagnosis. In their opinion all adults who are suffering from atrial septal defect and who have symptoms should undergo this operation, and that when the operative risk has diminished still further probably all cases should be treated surgically. *J. R. Belcher*

Mitral Valvular Disease Associated with an Inter-atrial Communication. Y. BOUVRAIN and A. SIBILLE. *Sem. Hôp. Paris*, **30**, 3414–3424, Oct. 6, 1954.

Reviewing 91 cases of mitral valvular disease associated with an interatrial communication collected from the literature, together with 5 of their own previously reported with Soulié (*Arch. Mal. Coeur*, 1954, **47**, 97), the authors stress the need for accurate diagnosis of the condition in view of the recently acquired possibility of surgical treatment. It is shown that a persistent ostium secundum (ovale) is three times as common as a persistent ostium primum, and that the mitral valve is affected by endocarditis twice as frequently as by a congenital abnormality. The clinical features were found to vary widely; signs of the septal defect may be clear or absent, while those of mitral disease are often diminished by the presence of the first lesion. Fluoroscopy is of paramount importance, and shows almost invariable enlargement of the heart, especially of the right side, pulsatile expansion of the median arc with dilatation of the pulmonary arteries, a small aorta, and backward compression of the œsophagus, the heart being sometimes pyriform and median as in pericarditis; yet the influence of mitral stenosis on this picture is negligible.

Cardiographic findings were available in one-third of the cases described. All except three revealed right-sided preponderance, but the incidence of right bundle-branch block could not be determined. Cardiac catheterization, in the few cases in which it was employed, gave conclusive evidence of the presence of septal defect, whereas angiocardiography was of little help. The authors point out that if auscultation yields unequivocal evidence of mitral stenosis the septal defect can readily be diagnosed; serious difficulty arises, however, when the septal defect is undoubted but the signs of mitral disease are inconclusive. In the 96 cases reviewed death, at an average age of 40 years, was usually due to congestive heart failure, but infants may die from pulmonary œdema. One of the patients described survived to the age of 82. *R. S. Stevens*

Pulmonic Valvular Stenosis. Results and Technique of Open Valvuloplasty. H. SWAN, H. C. CLEVELAND, H. MUELLER, and S. G. BLOUNT. *J. thorac. Surg.*, **28**, 504–515, Nov., 1954.

Pulmonary stenosis, whether in combination with a patent interatrial septum or as an isolated lesion, is not a benign condition, and the present authors recommend surgical treatment in all cases in which the systolic blood pressure in the right ventricle exceeds 75 mm. Hg. They note that the results obtained with the "blind" approach are unpredictable, the pressure gradient across the stenosed area often remaining high despite an apparently adequate operation. They have also been dissatisfied with the results of operation by the transventricular route, and have therefore developed a method whereby the pulmonary valve can be divided under direct vision through the pulmonary artery. They describe the technique in detail; in essence it consists in opening the pulmonary artery under hypothermia after the aorta has been clamped and the venæ cavæ occluded with tapes. The valve can be clearly seen and two incisions are made at 180 degrees to each other from the valve opening right out to the ring, this forming a sort of biscuspid valve. A finger should always be passed through the valve into the ventricle to confirm the absence of infundibular stenosis.

Of 7 patients operated on at the University of Colorado School of Medicine, Denver, by this technique, all have survived, and the postoperative catheterization studies have shown that the results, as judged by determination

of pressure gradients, are better than those in cases in which the blind technique was used. *J. R. Belcher*

Absence of the Left Pulmonary Artery. A Report of Six Cases with Autopsy Findings in Three. J. S. McKim and F. W. Wiglesworth. *Amer. Heart J.*, **47**, 845–859, June, 1954.

The authors report, from the Children's Memorial Hospital (McGill University), Montreal, 3 cases of absence of the left pulmonary artery confirmed at necropsy and 3 presumptive cases in patients still living (all aged 5 years), and on the basis of these and 11 cases reported in the literature in which the absence of one or other pulmonary artery was found they discuss the anatomical, clinical, angiocardiographic, and radiographic features of this condition.

In practically all the reported cases the anomaly has been associated with some other form of congenital heart disease, particularly Fallot's tetralogy. As a rule the pulmonary artery has been absent on the side opposite to that of the aortic arch, so that when the left pulmonary artery is absent the aortic arch is usually right-sided.

Paul Wood

Additional Observations Concerning the Physiology of the Hypertension Associated with Experimental Coarctation of the Aorta. H. W. Scott, H. A. Collins, A. M. Langa, and N. S. Olsen. *Surgery*, **36**, 445–459, Sept., 1954.

In experiments carried out on 97 dogs at Vanderbilt University School of Medicine, Nashville, Tennessee, the carotid and femoral blood pressure was first measured periodically during 7 to 30 days by direct puncture of these arteries, after which aortic coarctation was produced either by bridging the gap in a divided aorta by anastomizing the cut end of the left subclavian artery to the distal portion of the aorta, or by excising part of the wall of the aorta and suturing the cut edges together to produce aortic narrowing. It was found that to produce hypertension the coarctation must reduce the diameter of the aorta by 60 to 80 per cent.

Observation showed that a coarctation above the origin of the renal arteries was followed, after a latent interval of 4 to 5 days, by a gradual increase in carotid arterial pressure, the mean femoral arterial pressure, after an initial depression, also being increased. Constriction of the aortic isthmus was followed by an immediate rise in blood pressure, but this disappeared within 4 to 5 hours to give way to the gradual development of hypertension. The acute hypertension was therefore considered to be mechanical in origin. The chronic hypertension following coarctation of the aorta, however, is considered to be intimately concerned with the blood supply to the kidneys, since it occurred only if the aortic constriction was above the origin of the renal arteries and was great enough severely to restrict renal blood supply, and did not arise if the aortic constriction was below the origin of the renal arteries. Further experiments showed that the hypertension regressed when one kidney was transplanted so that its blood supply was derived from the aorta above the site of constriction, although this occurred only if the remaining kidney was removed; moreover, regression of the hypertension did not occur if the transplanted kidney derived its blood supply from vessels below the constriction. There was also no demonstrable change in the level of brachiocephalic blood pressure when the aorta was compressed or even completely severed below the origin of the renal arteries. Bio-assay of renal venous blood of some of the animals rendered hypertensive in this manner seemed to suggest that a pressor substance, "phirentasin", was circulating in the blood and that this disappeared when the hypertension regressed. It is concluded that these experiments confirm that the kidneys are intimately concerned in the production and maintenance of the hypertension associated with coarctation of the aorta.

H. E. Holling

Oral Administration of a Potent Carbonic Anhydrase Inhibitor ("Diamox"). I. Changes in Electrolyte and Acid–Base Balance. A. Leaf, W. B. Schwartz, and A. S. Relman. *New Engl. J. Med.*, **250**, 759–764, May 6, 1954.

"Diamox" (2-acetylamine-1 : 3 : 4-thiadiazole-5-sulphonamide), a highly potent, relatively non-toxic inhibitor of carbonic anhydrase, was given by mouth to 5 patients with congestive heart failure and one normal subject in doses ranging from 0·25 to 3 g. a day. In all 6 subjects there was an immediate rise in urinary *p*H, a fall in excretion of titratable acid and ammonium, and an increased excretion of water and potassium. Only in 3 subjects was there a sodium diuresis and in none a significant chloride diuresis. A slight or moderate loss of weight occurred in 5 patients. None developed hypokalæmia, but hyperchloræmic acidosis occurred in all 6 subjects and persisted throughout the period of treatment despite the fact that the composition of the urine became restored to control values within a few days of starting treatment. This restoration was attributed to the reduction in filtered bicarbonate resulting from the initial bicarbonate diuresis, which "would obligate less hydrogen ions in the reabsorption of bicarbonate and might therefore permit restoration of titratable acid and ammonium excretion with the same reduced over-all exchange of hydrogen".

K. G. Lowe

The Interplay of Coronary Vascular Resistance and Myocardial Compression in Regulating Coronary Flow. C. J. Wiggers. *Circulat. Res.*, **2**, 271–279, May, 1954.

A study of the phasic flow curves derived from the coronary sinus in dogs indicates that venous blood from the areas of the heart supplied by both right and left coronary arteries drains into the coronary sinus. By comparing the coronary sinus flow during systole plus the period of isometric contraction with that during the rest of diastole it was found possible to assess the extent to which coronary flow is influenced by variations in the force of ventricular contraction and in coronary vascular resistance. The author's findings suggest that the main effect of ventricular compression is not to reduce coronary flow but to improve it, possibly by a massaging action.

[This paper is difficult to compress and should be read in full.] *C. Bruce Perry*

THE EFFECTS OF 1-HYDRAZINOPHTHALAZINE ON THE PULMONARY CIRCULATION IN MITRAL DISEASE

BY

J. D. AITCHISON, W. I. CRANSTON, AND ELIZABETH A. PRIEST

From the Royal Infirmary, Aberdeen

Received November 9, 1954

During the investigation of the effects of hypotensive agents on the pulmonary circulation in mitral stenosis, an unexpected result was observed following the administration of 1-hydrazinophthalazine (apresoline). It was found that in patients with mitral stenosis, this drug caused elevation of the pulmonary arterial pressure, while reducing the systemic arterial pressure. This effect of

As already announced, the Second European Congress of Cardiology will be held at Stockholm, September 10–14, 1956. Those wishing to give communications must submit them through their national Cardiac Societies, and abstracts of such communications (about 250 words in length) should be sent to the Secretary, British Cardiac Society, 123, Alleyn Park, West Dulwich, S.E.21, before Monday, February, 27, 1956.

local anæsthesia with the patient supine, a cardiac catheter was introduced into the pulmonary artery, and 20–30 minutes were allowed for stabilization. Basal readings of mean pulmonary arterial pressure were obtained, using a saline manometer. The zero level was taken as a plane 5 cm. below the manubriosternal junction.

An initial determination of cardiac output was carried out at this time using the Fick principle. An arterial blood sample was withdrawn from the brachial or femoral artery, and a mixed venous sample from the pulmonary artery. Blood oxygen content was measured in duplicate on each sample by the method of Roughton and Scholander (1943). Oxygen uptake was measured over a period of 3–5 min., using a Benedict-Roth spirometer.

An injection of 10–20 mg. of 1-hydrazinophthalazine was then made slowly through the catheter. Mean pulmonary arterial pressure, systemic arterial pressure (by sphygmomanometer) and pulse or ventricular rate were measured frequently. The intervals between successive observations varied from 30 seconds, when values were changing rapidly, to several minutes. Further determinations of cardiac output were made, one about the time of maximal effect of the drug. Repeated determinations of pulmonary " capillary " pressure were not made because of the difficulty of ensuring that the catheter tip was wedged in the same site on each occasion. In one subject (E.T.) cardiac output was not measured, for technical reasons.

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Material

Twelve patients, aged 26 to 68, were investigated. Ten were suffering from rheumatic heart disease affecting the mitral valve, without other valvular involvement, and were in process of assessment for valvotomy. The predominance of stenosis or incompetence was assessed clinically and has been confirmed at operation in several cases. None was in heart failure at the time of observation. Two subjects were suffering from essential hypertension, and showed some elevation of pulmonary arterial pressure at rest; neither of these showed any evidence of rheumatic heart disease.

Methods

Two hours before the investigation began, each patient received 500 mg. of procaine amide by mouth. One hour later, this dose was repeated and 0·2 g. of quinalbarbitone was given. Under local anæsthesia with the patient supine, a cardiac catheter was introduced into the pulmonary artery, and 20–30 minutes were allowed for stabilization. Basal readings of mean pulmonary arterial pressure were obtained, using a saline manometer. The zero level was taken as a plane 5 cm. below the manubriosternal junction.

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Total pulmonary resistance was calculated from the formula:

$$\text{Resistance (dynes/sec./cm.}^{-5}) = \frac{\text{mean pulmonary arterial pressure (mm.Hg)} \times 1332}{\text{cardiac output (ml./sec.)}}$$

It is realized that the validity of this procedure is not beyond question because it may not be accurate in the presence of vasomotor changes or turbulent flow across a stenosed valve: it has been used only as a rough index.

RESULTS

A typical result is shown in Fig. 1. The initial levels of pulmonary and systemic arterial pressures were 74 and 125/80 mm. Hg respectively. At this time, the cardiac output was 3·1 l./min, and total pulmonary resistance 1910 dynes./sec./cm.$^{-5}$

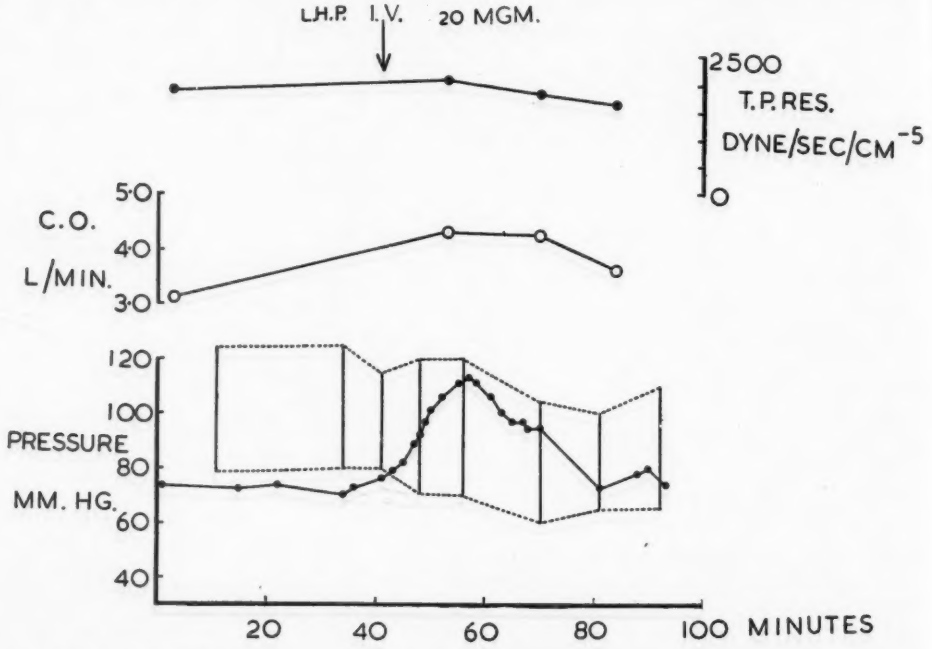

FIG. 1.—Subject M.D. 23/3/53. Response of pulmonary arterial pressure, systemic blood pressure, cardiac output, and total pulmonary resistance to 20 mg. 1-hydrazinophthalazine.

After administration of 1-hydrazinophthalazine the mean pulmonary arterial pressure rose rapidly, reaching a maximum value of 113 mm. Hg 16 minutes after the injection. At the same time the cardiac output rose to 4·3 l./min; during the next 35 minutes cardiac output and mean pulmonary artery pressure gradually fell, returning nearly to their control levels. The systemic pressure showed a gradual fall to a level of 100/65 mm. Hg during this time, but unlike the pulmonary arterial pressure, showed no sign of returning to the control level. The total pulmonary resistance showed a rise from 1910 to 2090 dyne./sec./cm.$^{-5}$ with a subsequent fall to 1640 dyne./sec./cm.$^{-5}$

A similar pattern was shown by 8 of the 9 patients with mitral disease; subject C. L. who had little if any stenosis of the valve and pulmonary arterial pressure and pulmonary resistance within

normal limits, showed an insignificant change in pulmonary arterial pressure and a slight decrease in total pulmonary resistance. The initial values, and values at the times of maximal observed pulmonary pressor effect in all subjects, are shown in Table I. The pulse rate rose in the 9 subjects in whom it was measured. The cardiac output also rose in all cases, though the increase was small, and of doubtful significance, in three. The increases in heart rate and in pulmonary artery pressure

TABLE I

INFLUENCE OF 1-HYDRAZINOPHTHALAZINE ON PRESSURES IN THE PULMONARY CIRCULATION AND ON CARDIAC OUTPUT

Subject	Age	Diagnosis	Rhythm	Pulmonary capillary pressure (mm. Hg)	Percentage alteration				Blood pressure	
					Pulmonary arterial pressure (mean)	Total pulmonary resistance	Cardiac output	Pulse	Cont.	L.H.P.
M.D. (F)	28	M.S. (c)	S	23·5	+53	+9	+39	–	125/80	100/75
M.B. (F)	46	M.S.	AF	21·7	+49	+11	+33	+47	135/100	130/95
I.M. (F)	44	M.S. (c)	S	11	+61	+50	+7	+57	125/80	120/75
M.W. (F)	38	M.S. (c)	A.F	18	+24	+16	+6	+33	120/75	105/60
E.T. (F)	47	M.S.	S	12·5	+84	—	—	+63	120/	90/
G.C. (M)	33	M.S., M.I.	AF	—	+44	+34·5	+7	+42	128/80	105/55
W.L. (M)	43	M.S., M.I.	AF	—	+73	+22	+42	+36	—	—
A.C. (F)	30	M.S., M.I.	S	26	+40	+16	+20	+45	105/65	100/50
J.J. (F)	52	M.S., M.I. (c)	AF	13·2	+47	+43·4	+3	+48	135/80	100/65
C.L. (F)	26	M.I.	S	—	+13	−17	+38	+23	150/80	150/80
A.G. (M)	61	H.T.	S	13	+4·5	−17	+28	+18	190/130	174/130
C.W. (M)	68	H.T.	S	—	−17	−51	+26	+7	230/130	120/64

M.S.=mitral stenosis. H.T.=hypertension. M.I.=mitral incompetence. S=sinus rhythm. (c) indicates confirmed at operation. AF=atrial fibrillation.

Dosage of L.H.P. 20 mg. except in Cases I.M. and A.C. in which it was 15 and 10 mg. respectively.

began about six minutes after the drug had been given. In most cases the maximum change in heart rate and pulmonary artery pressure occurred close to one another; the times of maximum effect varied from 10 to 50 minutes in different patients. The rise in pulmonary arterial pressure lasted for periods of 35 to 80 minutes; the tachycardia and systemic blood pressure fall were of rather longer duration, particularly in two cases. A fall in systemic blood pressure was observed in all patients except C.L.; in two patients the fall was so small as to be insignificant.

A severe fall in systemic blood pressure induced by 1-hydrazinophthalazine, as mentioned by Werko *et al.* (1954), was encountered in one case, examined late in the series; the investigation was terminated when the patient developed severe hypotension, and has not been included in the series. Apart from this, the only ill effect noted was the development of widespread pulmonary crepitations, suggestive of incipient pulmonary œdema, at the time when the pulmonary artery pressure was at its highest level, in subjects M.B. and E.T.

The increase in pulmonary arterial pressure was related to the initial level of pulmonary arterial

Total pulmonary resistance was calculated from the formula:

$$\text{Resistance (dynes/sec./cm.}^{-5}) = \frac{\text{mean pulmonary arterial pressure (mm.Hg)} \times 1332}{\text{cardiac output (ml./sec.)}}$$

It is realized that the validity of this procedure is not beyond question because it may not be accurate in the presence of vasomotor changes or turbulent flow across a stenosed valve: it has been used only as a rough index.

RESULTS

A typical result is shown in Fig. 1. The initial levels of pulmonary and systemic arterial pressures were 74 and 125/80 mm. Hg respectively. At this time, the cardiac output was 3·1 l./min, and total pulmonary resistance 1910 dynes./sec./cm.$^{-5}$

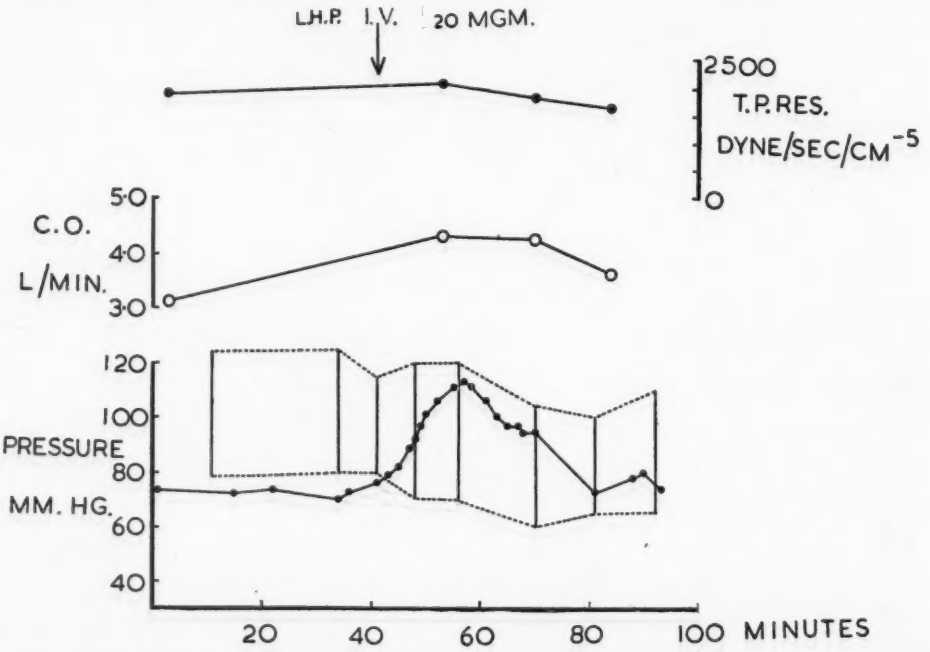

FIG. 1.—Subject M.D. 23/3/53. Response of pulmonary arterial pressure, systemic blood pressure, cardiac output, and total pulmonary resistance to 20 mg. 1-hydrazinophthalazine.

After administration of 1-hydrazinophthalazine the mean pulmonary arterial pressure rose rapidly, reaching a maximum value of 113 mm. Hg 16 minutes after the injection. At the same time the cardiac output rose to 4·3 l./min; during the next 35 minutes cardiac output and mean pulmonary artery pressure gradually fell, returning nearly to their control levels. The systemic pressure showed a gradual fall to a level of 100/65 mm. Hg during this time, but unlike the pulmonary arterial pressure, showed no sign of returning to the control level. The total pulmonary resistance showed a rise from 1910 to 2090 dyne./sec./cm.$^{-5}$ with a subsequent fall to 1640 dyne./sec./cm.$^{-5}$

A similar pattern was shown by 8 of the 9 patients with mitral disease; subject C. L. who had little if any stenosis of the valve and pulmonary arterial pressure and pulmonary resistance within

normal limits, showed an insignificant change in pulmonary arterial pressure and a slight decrease in total pulmonary resistance. The initial values, and values at the times of maximal observed pulmonary pressor effect in all subjects, are shown in Table I. The pulse rate rose in the 9 subjects in whom it was measured. The cardiac output also rose in all cases, though the increase was small, and of doubtful significance, in three. The increases in heart rate and in pulmonary artery pressure

TABLE I

INFLUENCE OF 1-HYDRAZINOPHTHALAZINE ON PRESSURES IN THE PULMONARY CIRCULATION AND ON CARDIAC OUTPUT

Subject	Age	Diagnosis	Rhythm	Pulmonary capillary pressure (mm. Hg)	Percentage alteration				Blood pressure	
					Pulmonary arterial pressure (mean)	Total pulmonary resistance	Cardiac output	Pulse	Cont.	L.H.P.
M.D. (F)	28	M.S. (c)	S	23·5	+53	+9	+39	—	125/80	100/75
M.B. (F)	46	M.S.	AF	21·7	+49	+11	+33	+47	135/100	130/95
I.M. (F)	44	M.S. (c)	S	11	+61	+50	+7	+57	125/80	120/75
M.W. (F)	38	M.S. (c)	A.F	18	+24	+16	+6	+33	120/75	105/60
E.T. (F)	47	M.S.	S	12·5	+84	—	—	+63	120/	90/
G.C. (M)	33	M.S., M.I.	AF	—	+44	+34·5	+7	+42	128/80	105/55
W.L. (M)	43	M.S., M.I.	AF	—	+73	+22	+42	+36	—	—
A.C. (F)	30	M.S., M.I.	S	26	+40	+16	+20	+45	105/65	100/50
J.J. (F)	52	M.S., M.I. (c)	AF	13·2	+47	+43·4	+3	+48	135/80	100/65
C.L. (F)	26	M.I.	S	—	+13	−17	+38	+23	150/80	150/80
A.G. (M)	61	H.T.	S	13	+4·5	−17	+28	+18	190/130	174/130
C.W. (M)	68	H.T.	S	—	−17	−51	+26	+7	230/130	120/64

M.S.=mitral stenosis. H.T.=hypertension. M.I.=mitral incompetence. S=sinus rhythm. (c) indicates confirmed at operation. AF=atrial fibrillation.

Dosage of L.H.P. 20 mg. except in Cases I.M. and A.C. in which it was 15 and 10 mg. respectively.

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The increase in pulmonary arterial pressure was related to the initial level of pulmonary arterial

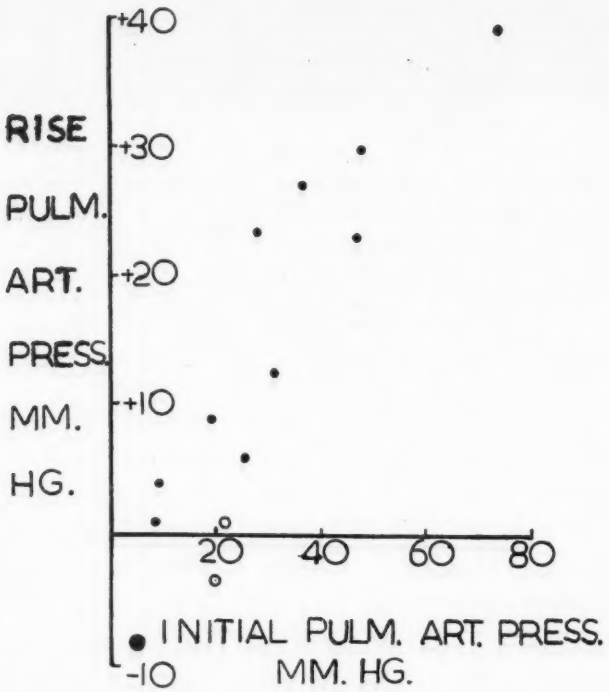

FIG. 2.—Relationship between initial level of pulmonary arterial pressure and rise of pulmonary arterial pressure after administration of 1-hydrazinophthalazine. Closed circles indicate subjects with mitral disease, open circles hypertensive subjects.

pressure (Fig. 2). Subjects with a high control level showed a greater increase than those in whom the basal level was low. In this and subsequent figures the closed circles represent patients with mitral disease, and the open circles represent the values obtained in the two hypertensive subjects. In one of the hypertensives there was a fall in pulmonary arterial pressure with a large fall in systemic blood pressure. In the other the rise in pulmonary artery pressure was much smaller than that observed in the mitral patients with comparable pulmonary arterial pressures. In both cases the cardiac output rose after 1-hydrazinophthalazine; the pulse rate also increased but the rise was less than in the patients with mitral disease.

DISCUSSION

The principal factors that may be concerned in the rise of pulmonary arterial pressure are pulmonary vasoconstriction, increase in cardiac output, and increase in pulse rate. In the absence of information about changes in the pulmonary " capillary " pressure, the part played by possible constriction of the pulmonary arterioles cannot be assessed. The development of incipient pulmonary œdema in two subjects suggests that, in them at least, the pulmonary " capillary " pressure rose following the administration of the drug. If this were true of all cases, it would indicate that vasoconstriction, if it occurred at all, was not the only factor responsible for the increase in pulmonary hypertension. Araujo and Lukas (1952) found large increases in pulmonary " capillary "

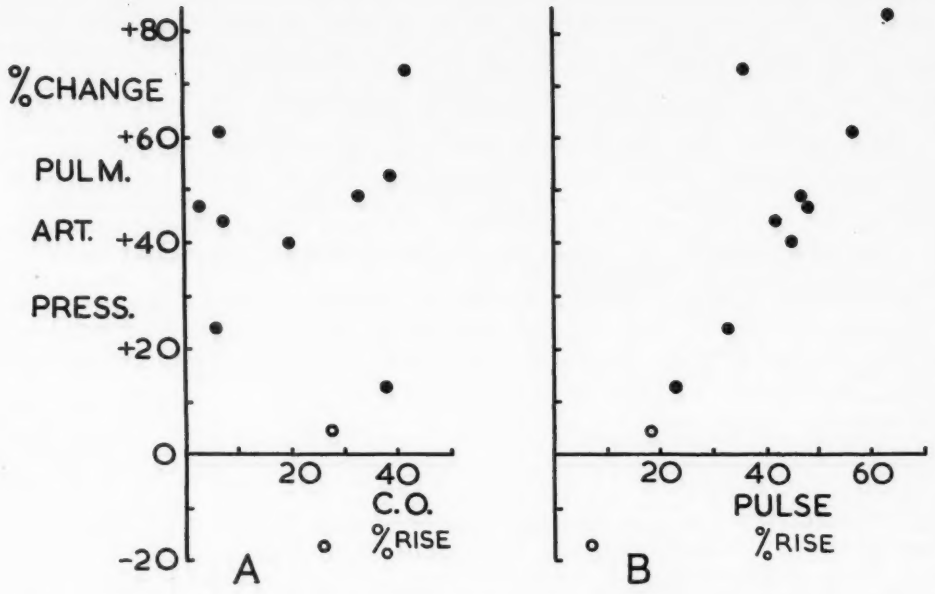

FIG. 3.—A. Percentage increase in pulmonary arterial pressure plotted against percentage increase in cardiac output. B. Percentage increase in pulmonary arterial pressure plotted against percentage increase in pulse rate. Closed circles represent subjects with mitral disease, open circles hypertensive subjects.

pressure in mitral stenosis during exercise, which were not prevented by increased pulmonary vascular (arteriolar) resistance.

Cardiac output was increased in all our subjects, though the increase was very small in three. In normal subjects undertaking exercise the pulmonary artery pressure does not rise above the upper limit of normal until the flow exceeds approximately three times the basal flow (Cournand, 1950). This implies that vasodilatation occurs in the pulmonary system of normal subjects with exercise. In mitral stenosis the capacity to tolerate an increased cardiac output is impaired, so that, even where there is little or no pulmonary hypertension at rest, a moderate degree of effort commonly causes a distinct rise in pulmonary arterial pressure. In Fig. 3 the percentage increase in cardiac output in our cases is plotted against the percentage increase in pulmonary arterial pressure. There is no relationship between the two variables ($r=+0{\cdot}132$, $p>0{\cdot}10$). This argues against the pressure rise being simply a manifestation of increased flow through a relatively inflexible pulmonary vascular system, although the increased output probably plays a part in some cases. It is also evident from Table I that a high initial pressure or resistance is not necessarily associated with inability to raise the cardiac output in response to administration of 1-hydrazinophthalazine.

It is probable that in mitral stenosis the whole period of diastole following the opening of the mitral valve is taken up with inflow into the ventricle (Wiggers, 1923). This contrasts with the state of affairs in normal subjects, in whom most of the ventricular filling takes place early in diastole. Increase in pulse rate from 80 to 140 may shorten the duration of diastole by as much as 12 seconds each minute (Gorlin *et al.*, 1951). In mitral stenosis in such circumstances cardiac output can only be maintained or augmented by increasing the rate of flow through the valve during diastole; this in turn means that the pressure gradient across the valve must increase, so that back pressure develops in the pulmonary vascular system. In this series the increase in pulse rate at the time of

maximal pulmonary arterial pressure was significantly related to the rise in pulmonary arterial pressure ($r = +0{\cdot}761$, $p < 0{\cdot}02$). Tachycardia may not be the whole explanation for the pressure rise, because in some subjects the tachycardia lasted rather longer than the rise in pulmonary artery pressure. The degree of tachycardia was noticeably less in the two cases of hypertension. The response was not related to the type of rhythm, and it is interesting to observe that the increase in heart rate in subjects with atrial fibrillation was similar to the rise in subjects in sinus rhythm. The hypertensive effect of 1-hydrazinophthalazine on the pulmonary circulation of subjects with mitral disease is probably the result of the interaction of several factors, of which the most important seem to be the degree of initial pulmonary hypertension and the degree of tachycardia following the administration of the drug. It has been stated that the incidence of hypertension in mitral stenosis is not significantly different from that in a control hospital population (Gray, 1954), and in a few instances, hypertension may be the cause of death.

The results of this investigation suggest that the use of 1-hydrazinophthalazine is contraindicated in mitral disease, as it raises cardiac rate and output and pulmonary arterial pressure, so increasing the load on the right ventricle. It may predispose towards the development of pulmonary œdema.

Summary

Administration of 1-hydrazinophthalazine to ten patients with mitral disease was followed by elevation of the pulmonary arterial pressure, increased pulse rate and cardiac output, and fall in systemic blood pressure.

It is suggested that 1-hydrazinophthalazine should not be used in the treatment of hypertension associated with mitral disease, as it is likely to increase the load on the right ventricle, and may even cause pulmonary œdema.

We are grateful to Dr. R. J. Duthie for encouragement and for permission to investigate patients under his care. We wish to thank Dr. T. N. Morgan for helpful criticism. Apresoline was kindly supplied by Mr. J. Lawrie of Ciba Laboratories.

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THE PRODUCTION OF BLOCK AND AURICULAR FIBRILLATION IN THE HEART–LUNG PREPARATION BY INHIBITORS OF CHOLINESTERASE

BY

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As a result of the work of Otto Loewi it was discovered that the effects of vagal stimulation were transmitted to the heart by the release of acetylcholine. This substance itself when introduced into the circulation is known to have a powerful inhibitory action on both the rate and the force of the heart beat. Evidence has recently accumulated that, in addition to these inhibitory actions, acetylcholine has effects that may be regarded as excitatory. It is possible, indeed, that the inhibitory and excitatory effects of acetylcholine may be of significance in maintaining the normal rhythm of the heart. The evidence for this view is as follows. The heart contains not only acetylcholine itself, but the appropriate mechanisms for its synthesis by choline acetylase from choline (Comline, 1946), and for its destruction by cholinesterase (Ord and Thompson, 1950). It was found (Bülbring and Burn, 1949) that if rabbit auricles were allowed to beat in a bath of Ringer's solution until they stopped, the addition of acetylcholine caused the beat to start again. It was also found that choline acetylase activity was high in fresh rabbit auricles, but declined to a low value when the auricles were kept in a bath until they ceased to beat. When such non-beating auricles were restarted with acetylcholine it was found that their ability to synthesize acetylcholine had also been restored. These observations have led to further investigations of the part played by acetylcholine. The isolated rabbit heart perfused with Ringer's solution has been found to liberate acetylcholine in the perfusate so long as contractions continued, but if the beat was arrested, by perfusing either with Ca-free Ringer, or by adding dinitrophenol to the perfusing fluid, acetylcholine was no longer liberated (Briscoe and Burn, 1954).

If acetylcholine plays a part in the maintenance of the normal rhythm, it is presumably destroyed by cholinesterase, and inhibitors of that enzyme should modify the rhythm. For a study of such an effect the Starling heart–lung preparation is suitable, since the heart is free from central control by the vagi and the sympathetic nerves. An account has already been published of the effect of cholinesterase inhibitors in reducing the rate of the beat in the heart–lung preparation of the dog (Burn and Walker, 1954). Concentrations of eserine, neostigmine, and other substances in the range 10^{-6}M to 10^{-5}M were found to lower the rate to about 60 to 70 per cent of its initial value, and the rate was rapidly restored by injections of small amounts of atropine.

We have now studied the effect of these inhibitors on the P–R interval and on the A-V block when the heart–lung preparation is driven electrically at increasing rates. We have also studied their effect on output at constant rate. Finally, we have studied the conditions in which they produce auricular fibrillation.

METHODS

The methods have been described recently (Burn *et al.*, 1955*a*) and need only be summarized briefly. The heart–lung preparation of a dog was made (Knowlton and Starling, 1912). Heparin was used to prevent clotting. Electrodes were applied to the tip of the right auricle and held in position by a spring clip.

The electrodes did not pierce the tissue and trauma was reduced to a minimum. Stimuli of 1 mA strength and 0·9 msec. duration were used. Leads to a Cossor electrocardiograph (model 1314) were taken from the right and left forelegs and left hindleg after removing a patch of skin. The inhibitors of cholinesterase (ChE) which were studied included eserine sulphate; neostigmine (prostigmin methylsulphate); paraoxon (E.600 or mintacol), which is diethyl-*p*-nitrophenylphosphate; Nu 683, which is the dimethylcarbamate of (2-hydroxy-5-phenylbenzyltrimethyl) ammonium bromide; and B.W.284,C.51, which is the dimethobromide of 1 : 5-di (*p*-N-allyl-N-methylaminophenyl)-pentan-3-one.

Results

Cholinesterase Inhibitors on the P–R Interval. The duration of the P–R interval was found to be increased by inhibitors of cholinesterase in the heart–lung preparation even when the heart was beating spontaneously. Observations from seven experiments are recorded in Table I, in which the corresponding heart rates are also shown. In Experiment 1 the initial heart rate was 142 per min. and the P–R interval was 84 msec. In the presence of eserine 2×10^{-6}M the heart rate was reduced to 134 per min. and the P–R interval was increased to 120 msec. In Experiment 10 the initial rate was 141 per min. and the P–R interval was 84 msec. Neostigmine was then added to the reservoir first in the concentration of $0{\cdot}6 \times 10^{-6}$M and later in the concentration $1{\cdot}8 \times 10^{-6}$M. This final concentration reduced the spontaneous rate to 84 per min., and lengthened the P–R interval to 136 msec. Finally, the injection of 20 μg. atropine raised the spontaneous rate to 150 per min. and reduced the P–R interval to 80 msec., that is to say, restored the initial values. The other experiments in Table I demonstrate a similar lengthening of P–R interval accompanied by slowing of the spontaneous rate, produced by eserine, by Nu 683, and by paraoxon, the effects in Experiments 16 and 21 being proportional to the concentration of inhibitor added.

TABLE I

Effect of ChE Inhibitors and Atropine on P–R Interval during the Spontaneous Rhythm

Experiment	Substance added	Concentration	P–R interval (msec.)	Heart rate (per min.)
1	None	—	84	142
	Eserine	2×10^{-6}M	120	134
2	None	—	96	183
	Eserine	2×10^{-6}M	120	98
8	None	—	76	172
	Eserine	$1{\cdot}5 \times 10^{-5}$M	128	59
	Atropine	6×10^{-6}g./ml.	80	157
10	None	—	84	141
	Neostigmine	$0{\cdot}6 \times 10^{-6}$M	108	116
	,,	$1{\cdot}8 \times 10^{-6}$M	136	84
	Atropine	2×10^{-6}g./ml.	80	150
11	None	—	116	117
	Neostigmine	$4{\cdot}5 \times 10^{-6}$M	152	76
	Atropine	$0{\cdot}5 \times 10^{-7}$g./ml	92	138
16	None	—	84	125
	Paraoxon	9×10^{-6}M	108	96
	,,	$1{\cdot}8 \times 10^{-5}$M	124	74
	,,	$3{\cdot}6 \times 10^{-5}$M	132	73
	Atropine	$0{\cdot}7 \times 10^{-7}$g./ml.	80	126
21	None	—	80	146
	Nu 683	10^{-6}M	88	134
	,,	2×10^{-6}M	112	125
	Neostigmine	$4{\cdot}5 \times 10^{-6}$M	164	119
	,,	9×10^{-6}M	172	113

Acetylcholine Infusion on the P–R Interval. In order to compare the results in Table I with those obtained during the infusion of acetylcholine at a constant rate into the blood entering the heart–lung preparation through the superior vena cava, figures are given in Table II for six experiments in which the amounts infused were from 100 to 400 μg. per min. It can be seen that in every experiment the infusion of acetylcholine produced a lengthening of the P–R interval. The actual amount of acetylcholine required to produce a given percentage change in P–R interval varied greatly from dog to dog. For example, the infusion of 400 μg. acetylcholine per min. in Experiment 9 prolonged the P–R interval only from 112 to 124 msec.; the same rate of infusion in Experiment 28 prolonged the P–R interval from 80 msec. to 164 msec. The effect of acetylcholine infusions in slowing the pacemaker (Burn, *et al.*, 1955*a*) exhibited a similar wide range of dose response, and may be related to the amount of circulating cholinesterase.

TABLE II
EFFECT OF INFUSION OF ACETYLCHOLINE ON P–R INTERVAL

Experiment	Control P–R (msec.)	Rate of ACh infusion per min. (μg.)	P–R during infusion (msec.)
6	76	200	96
9	112	400	124
13	84	100 200	96 100
14	92	100	94
15	104	100 200 400	112 120 140
28	80	400	164

Production of Complete A-V Block. The slowing of conduction from the auricle to the ventricle became sufficient to produce complete block when higher concentrations of cholinesterase inhibitors were used. In Experiment 18, paraoxon in concentration $1{\cdot}8 \times 10^{-5}$M caused complete dissociation of auricles and ventricles, the former contracting about 81 per min., and the latter about 37 per min. Electrical stimulation of the auricle then had no effect on the ventricular rate. A slightly higher concentration of paraoxon ($2{\cdot}7 \times 10^{-5}$M) had the same effect in Experiment 19, when the auricles contracted at 58 per min. and the ventricles at 37 per min. (see Fig. 1). In this experiment also, electrical stimulation of auricles up to 720 per min. did not modify the ventricular rate. Eserine in concentrations of $1{\cdot}5 \times 10^{-5}$M and 3×10^{-5}M in other experiments also produced a complete block.

Effect of Inhibitors on Output. To determine the effect of inhibitors of cholinesterase on output, it was necessary to exclude the effect on the heart rate. A series of observations were therefore made in which the heart was driven electrically at various rates so that the output at a given rate could be compared in the absence of an inhibitor, in its presence, and after the addition of atropine. In some experiments the output fell gradually due to deterioration of the preparation, and the results in Table III have been selected from those experiments in which there was little deterioration. All the results were obtained at rates at which the ventricles followed every beat of the auricles. Table III shows that in three experiments in which eserine, neostigmine, and paraoxon respectively were used, the output in the presence of the inhibitor was less than in the control period, and was also less than in the subsequent period after atropine was given. Experiments 12 and 14 also show that the fall in output due to the presence of the inhibitor was progressively greater at greater rates. The infusion of acetylcholine when the heart was driven at constant rate also caused a fall in output (Burn *et al.*, 1955*a*).

The Effect of a Period of Electrical Stimulation. The observations thus far described have shown that inhibitors of cholinesterase slow the spontaneous rate of the heart–lung preparation, increase the P–R interval, and reduce the output of blood at a given rate, and that these three effects are abolished by atropine.

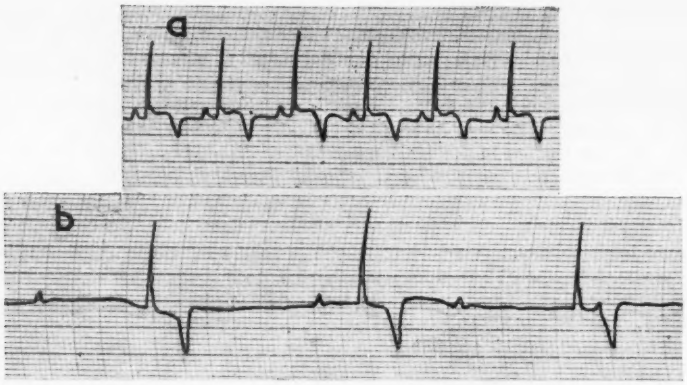

FIG. 1.—Cardiogram of dog heart–lung preparation, (a) in presence of paraoxon 9×10^{-6} molar, the rate was slowed to 112 per min.; (b) in presence of paraoxon $2{\cdot}7 \times 10^{-5}$ molar there was complete block, the auricles and ventricles contracting independently.

TABLE III

EFFECT OF ChE INHIBITORS ON OUTPUT AT CONSTANT RATE

Experiment	ChE inhibitor	Concentration	Driving rate	Output (ml./15 sec.)		
				Control	In presence of inhibitor	After atropine
9	Eserine	$0{\cdot}45 \times 10^{-6}$M	170/min.	152	126	150
12	Neostigmine	$4{\cdot}5 \times 10^{-6}$M	238	202	160	170
	,,	,,	248	182	112	166
14	Paraoxon	9×10^{-6}M	190	186	150	156
	,,	,,	202	192	126	146
	,,	,,	216	192	90	120
	,,	,,	225	186	52	92

The observations form a suitable prelude to a consideration of the effect of driving the heart electrically. Each period of driving was of similar length and was carried out according to a fixed routine. Stimulation was first applied at a rate about 20 per min. faster than the spontaneous rate. The stimulation was continued for about 40 seconds, during which a cardiogram was taken and the output was measured. Without stopping the stimulation the rate was increased by about 10 per cent and the observations were repeated. In this way the rate was increased up to 550 per min. and the stimulation was then stopped. An electrocardiogram was taken and the output was measured. A pause was then made for about 6–9 min., when another record was taken and the output measured again. Results from a series of experiments are given in Table IV and they show that the spontaneous rate was always lower at the end of driving than it had been at the beginning, and that in a few minutes it rose again to approximately its original value. Similarly the P–R interval was always longer at the end of driving than it had been before, and after a few minutes it returned towards its normal value. Finally, the output was always less after driving than it had been before, and in a few minutes it increased again. Thus the effect of driving the heart electrically on the spontaneous rate, the P–R interval and the output was the same as the effect of adding an inhibitor of cholinesterase to the preparation when beating at its own rhythm. Moreover, the effect of driving lasted for a few minutes only. The inference is obvious that the procedure of driving may have produced an increased output of acetylcholine, which fell to its original level soon after stimulation was stopped. Further evidence on this will be presented subsequently.

TABLE IV

TO SHOW EFFECT OF A PERIOD OF ELECTRICAL STIMULATION

Results in the column " After " were obtained immediately after the period of electrical stimulation, and those in the column " Later " 2·5 to 9 min. later

Experiment	Spontaneous rate per min.				P–R interval (msec.)		Output (ml./15 sec.)		
	Before	After	Later	Before	After	Later	Before	After	Later
1	142	136	146	84	99	92	124	110	126
18	158	124	141	100	124	108	104	92	146
19	142	125	135	90	110	66	140	118	144
21	146	135	141	80	92	84	154	144	152
25	117	110	110	80	98	88	116	88	116
26	148	137	143	63	104	63	150	126	134
27	183	165	187	82	101	81	190	168	194

Action of Inhibitors during Electrical Stimulation. When the heart is driven electrically at increasing rates it is well known that at a certain critical rate a point is reached at which the ventricles no longer follow the auricles and some degree of A-V block begins. The presence of inhibitors of cholinesterase facilitated the appearance of such partial A-V block with great regularity.

In Fig. 2 the ventricular rate expressed as a percentage of the auricular rate is plotted as ordinate, and the rate of stimulation as abscissa. The ventricular rate remained the same as the auricular rate up to 300 stimuli per min., but above this the ventricular rate fell until it was 50 per cent of the auricular rate at 383 stimuli per min. The 2 : 1 block thus established persisted up to 550 stimuli per min. When eserine was added to make a concentration of $4{\cdot}5 \times 10^{-6}$M (1·35 mg. in 900 ml.), and the stimulation at increasing rates was repeated, block occurred at much lower rates, so that the whole curve was shifted to the left (Fig. 2, B). The ventricular rate fell below the auricular rate when the rate of stimulation was only 214 per min., and a 2 : 1 rhythm began at 274 stimuli per min. At 440 stimuli per min. the ventricular beats were 45 per cent of the auricular beats, and at 576 stimuli per min. the block was 4 : 1.

Stimulation was then stopped, and 30 μg. atropine was injected into the blood, entering the cannula in the superior vena cava. When stimulation at increasing rates was repeated for a third time, the ventricular rate followed the course it took during the first period of stimulation before eserine was added (Fig. 2, C). The small amount of atropine therefore abolished the action of eserine.

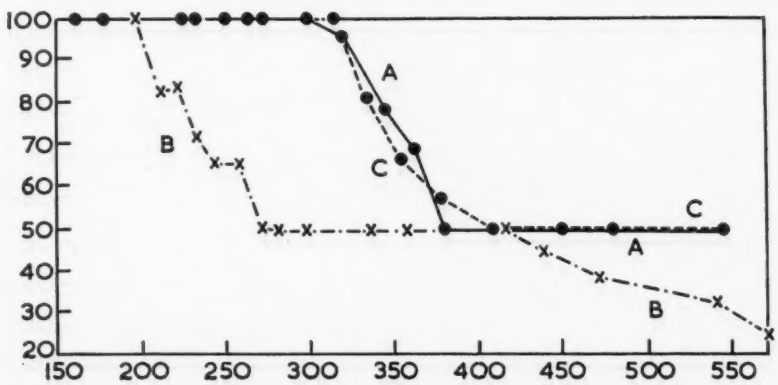

FIG. 2.—Heart–lung preparation driven by electrical stimulation. Abscissa: rate of stimulation per min. Ordinate: percentage of auricular beats transmitted to the ventricles. (A) Shows control observations; (B) shows observations in the presence of eserine $4{\cdot}5 \times 10^{-6}$ molar; (C) shows observations then made after the injection of 30 μg. atropine.

The Effect of Atropine. It has been shown that the injection of a small amount of atropine abolished the action of eserine in shifting the onset of block to a lower rate. It was of interest, therefore, to determine whether a larger amount of atropine might shift the curve to the right, i.e. to delay the onset of block until a higher rate of stimulation was reached. That this was, in fact, the case is shown in Experiment 10 of Table V, in which the presence of atropine $0{\cdot}3 \times 10^{-5}$g./ml. shifted the point of onset of block from 225 to 280 stimuli per minute, and the onset of 2 : 1 block from 270 to 350 stimuli per minute. Hexamethonium, on the other hand, had no effect upon the onset of block (Table V, Experiment 24).

TABLE V

CHANGE IN A-V CONDUCTION BY NEOSTIGMINE AND ATROPINE

Figures are rate/min. V = ventricular rate. A = auricular rate

Experiment	Conditions	Maximum rate of stimulation for V = A	Minimum rate of stimulation for V = ½A
10	First control	225	270
	Second ,,	215	281
	Third ,,	222	278
	Neostigmine		
	$0{\cdot}6 \times 10^{-6}$M	183	220
	$1{\cdot}8 \times 10^{-6}$M	83	108
	Atropine		
	$0{\cdot}3 \times 10^{-7}$g./ml.	254	305
	$0{\cdot}3 \times 10^{-5}$g./ml.	280	350
24	First control	298	384
	Second ,,	298	380
	Neostigmine		
	$3{\cdot}0 \times 10^{-6}$M	255	350
	Hexamethonium		
	10^{-5}g./ml.	261	345
	Atropine		
	$0{\cdot}5 \times 10^{-7}$g./ml.	300	366

The procedure of driving does not itself affect the rate at which block first makes its appearance. Evidence for this is also presented in Table V. In Experiment 10, there were three control periods of increasing stimulation, and in all three the rates of stimulation above which the ventricle began to miss beats, and at which the 2 : 1 rhythm developed were almost the same. In Experiment 24 there were two control periods.

The Effect of Block on Output. In a recent paper (Burn *et al.*, 1955*b*) direct experimental evidence was presented of the beneficial effect on cardiac output of the onset of A-V block or of auricular fibrillation. In the present series of experiments also it was found that when the heart was driven at increasing rates, the output of blood varied directly as the ventricular rate when that rate was low, and inversely as the ventricular rate when that rate was high. The onset of block therefore modified the output. An example is given in Fig. 3. Fig. 3*a* shows results obtained in the control period at the beginning of the experiment. As the ventricular rate rose to 286/min. the output fell from 194 ml./15 sec. to 22 ml./15 sec. When the ventricular rate fell as block began, the output rapidly recovered, and with higher rates of stimulation the record of its change was approximately the inverse of that of the ventricular rate. After the control observations were made, neostigmine was added, the concentration being $4{\cdot}5 \times 10^{-6}$M. When the heart was stimulated at increasing rates, the relation between ventricular rate and output was that shown in Fig. 3b. Owing to the early incidence of block, the ventricle ceasing to follow the auricle above 158 per min., the ventricular rate was throughout much slower, and the output of blood followed the ventricular rate closely. The fall in output seen in Fig. 3a at a rate of stimulation of 286/min. was absent. These observations illustrate the value of block in preventing a fall in output due to a too rapid ventricular rate. When the observations in the presence of neostigmine were complete, atropine was injected and the observations shown in Fig. 3c were made, which were very similar to those in Fig. 3a.

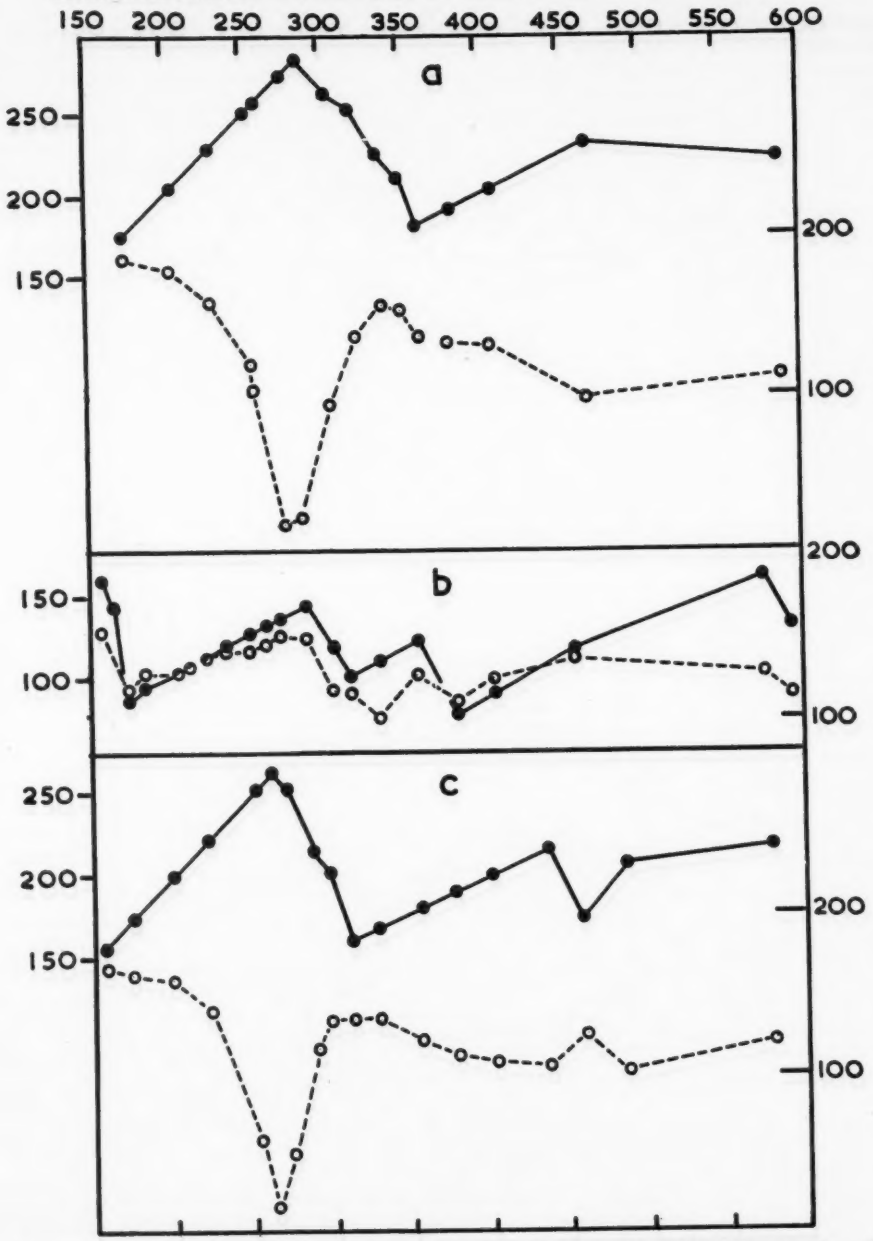

FIG. 3.—Heart–lung preparation driven by electrical stimulation. Abscissa: rate of stimulation per min. Ordinate: in all three parts of the figure, the ordinate on the left is the ventricular rate which is plotted as black circles with a continuous line; the ordinate on the right is the output of blood per 15 sec. which is plotted as white circles with a dotted line. (a) Shows control observations; (b) shows observations in the presence of neostigmine $4{\cdot}5 \times 10^{-6}$ molar; (c) shows observations after the injection of 50 μg. atropine.

Effect of Varying Concentrations. The effects of varying concentrations of an inhibitor were tested in several experiments. An example of the effects of varying concentrations of paraoxon is given in Fig. 4; each concentration has been calculated on the assumption that the paroxan at our disposal was 100 per cent pure and the concentrations may therefore have been less than stated; the relative values would remain the same. The concentrations are shown on the abscissa on a logarithmic scale; the ordinates are the rates of stimulation. Curve A indicates the effect of increasing concentrations of paraoxon on the maximum rate at which the ventricles followed the auricles. Curve B is the effect on the minimum rate at which a 2 : 1 rhythm was seen. Curve C is the effect on the maximum rate at which a 2 : 1 rhythm was seen, i.e. above this rate the block became greater than 2 : 1.

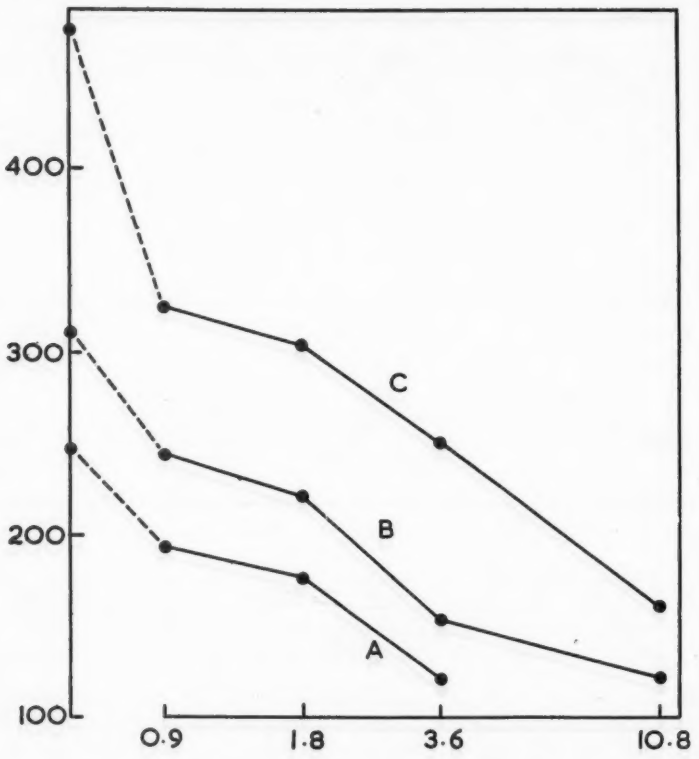

FIG. 4.—Heart–lung preparation driven electrically. Abscissa: concentration × 10^{-5} molar of paraoxon shown on a logarithmic scale. Ordinate: rate of stimulation per min. (A) Shows the maximum rate of stimulation at which the ventricles followed all contractions of the auricles; (B) shows the minimum rate of stimulation at which a 2 : 1 block was seen. (C) shows the maximum rate of stimulation for 2 : 1 block; at higher rates the block was more than 2 : 1. All these rates declined as the concentration of paraoxon rose.

Regularity of the Effect on Block. The effects described were produced with great regularity, as the list of observations given in Table VI shows. The only exception was when B.W.284.C.51 was used, which shifted the onset of block to a slightly higher rate in the two experiments in which it was tried. Recently Tedeschi (1954) has obtained evidence that several inhibitors of cholinesterase have an atropine-like action on cardiac tissue, and that B.W.284.C.51 possesses this action to a greater extent than do the others. He found that neostigmine also had some atropine-like action, and this may explain why we obtained a much

smaller effect than usual when we added as much as 6 mg. to 1 litre of blood at the beginning of one experiment. Tedeschi observed that the organic phosphate inhibitors such as paraoxon were without atropine-like action, and this substance always produced effects that increased with the concentration as shown in Fig. 4.

TABLE VI

EFFECT OF INHIBITORS OF ChE ON RATE OF STIMULATION AT WHICH BLOCK OCCURRED

Figures are rates per minute.

Experiment	Inhibitor	Molar concentration	Maximum rate at which V = A		Drop in rate
			Before inhibitor was added	In presence of inhibitor	
1	Eserine	2×10^{-6}	228	168	60
2	,,	,,	256	148	108
3	,,	3×10^{-6}	253	163	90
4	,,	$4{\cdot}5 \times 10^{-6}$	300	197	103
5	,,	,,	322	266	56
6	,,	,,	272	201	71
7	,,	9×10^{-6}	280	218	62
8	,,	$1{\cdot}5 \times 10^{-5}$	327	138	89
9	,,	$4{\cdot}5 \times 10^{-5}$	185	94	91
10	Neostigmine	$1{\cdot}8 \times 10^{-6}$	222	83	139
11	,,	$4{\cdot}5 \times 10^{-6}$	200	107	93
12	,,	,,	286	244	42
13	,,	,,	286	158	128
14	Paraoxon	9×10^{-6}	263	225	38
15	,,	,,	225	184	41
16	,,	,,	246	194	52
17	,,	,,	267	171	96
18	,,	,,	205	132	73
19	,,	,,	251	188	63
20	Nu 683	2×10^{-6}	268	232	36
21	,,	,,	246	198	48
22	284.C.51	$4{\cdot}5 \times 10^{-6}$	259	268	0
23	,,	,,	310	338	0

Speed of Onset of Block. In some experiments a study was made of the speed at which block developed when the auricle was stimulated at a high rate. By stimulating at increasing rates, a rate was determined at which a 4 : 3 or a 3 : 2 block was produced. The stimulation was then stopped, and after a few minutes it was begun again at that particular rate. A continuous electrocardiogram record was taken for about 2 minutes from the start of the stimulation. It was found that when the stimulation was applied the ventricle at first followed every beat of the auricle, and that thereafter block developed gradually as shown in Fig. 5(I). An inhibitor of cholinesterase was then added to the blood, and stimulation at the same rate was repeated. Fig. 5(II) shows the effect of 0·3 mg. eserine in 1 litre of blood, making a concentration 10^{-6}M. The speed of onset of the block was now much faster than before. Atropine was then injected and stimulation applied again; the speed of onset of block was rather less than in the control period, Fig. 5(III). These observations showed that the block present at any rate of stimulation depended to some extent on the length of time for which the stimulation had been applied, the full degree of block that the stimulus produced appearing in about one minute.

Effect of Stimulation on P–R Interval. When the heart was driven at increasing rates the P–R interval was observed to become longer, but the increase in the interval for a given increase in rate was greater in the presence of an inhibitor of cholinesterase. The observations in Fig. 6 taken from Experiment 10 were typical of those made in six experiments in which the P–R interval was measured. Curve 1 in Fig. 6 shows at the left end the P–R interval when the heart was beating spontaneously at the rate indicated. The four succeeding points were recorded during electrical stimulation. Curve 2 was obtained by repeating the rates of stimulation; all P–R intervals were longer but Curve 2 was approximately parallel to Curve 1. A third repetition of the rates of stimulation gave results coinciding with those in Curve 2. Neostigmine was then added to make a concentration of $0{\cdot}6 \times 10^{-6}$M, and in its presence the rates of stimulation were repeated

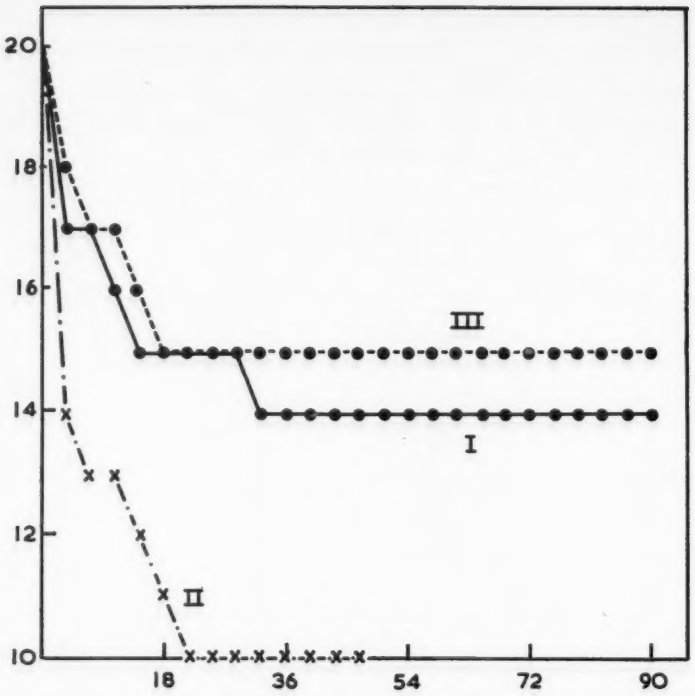

FIG. 5.—Heart–lung preparation of dog. Auricles stimulated at 330 per min. Abscissa: time in seconds from beginning of stimulation. Ordinate: number of stimuli transmitted to ventricles out of each successive 20 stimuli. Graph I shows control observations. Graph II shows observations in the presence of eserine 10^{-6} molar. Graph III shows observations after the injection of 0·2 mg. atropine.

for the fourth time. The results were those in Curve 3 which was approximately parallel to Curves 1 and 2 at its left end, but at its right end rose more steeply upwards. A further addition of neostigmine which brought the concentration to $1{\cdot}8 \times 10^{-6}$M caused the spontaneous rate to fall to 83 per min. (see Curve 4) and the P–R interval to rise to 134 msec.; when the heart was stimulated electrically at the same rate the P–R interval rose to 157 msec. Finally, atropine was injected, and Curve 5 was then obtained with shorter P–R intervals for a given rate of stimulation than those in Curve 1. These results were to be expected in view of the findings already described that (1) the presence of a ChE inhibitor increased the P–R interval when the heart was beating spontaneously in spite of slowing the rate, this increase being abolished by atropine, and that (2) the P–R interval was increased at the end of a period during which the heart was stimulated electrically at increasing rates.

Production of Cardiac Arrest. In some experiments, electrical stimulation in the presence of an inhibitor of cholinesterase led to ventricular arrest. Thus in one experiment the addition of neostigmine in concentration $1{\cdot}8 \times 10^{-6}$M reduced the spontaneous rate to 83 per min., and the ventricle ceased to follow all beats of the auricle during stimulation at so low a rate as 97 per min. When the rate of stimulation was 198 per min. there was a block of 6 : 1 as shown in Fig. 7a. When the rate was raised to 243 per min. there was not only complete block but also disappearance of all ventricular activity. The rate of stimulation was reduced (Fig. 7c) and then stimulation was stopped, at which point all cardiac activity ceased (Fig. 7d). An injection of 20 μg. atropine was made into the ventricle, and the ventricle was squeezed to drive the blood into the aorta and so to the coronary circulation. The first sign of recovery of activity was auricular

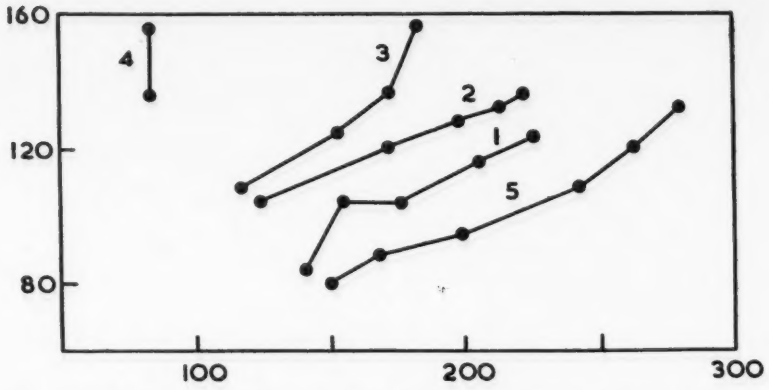

FIG. 6.—Heart–lung preparation. Abscissa: heart rate per min. Ordinate: duration of P–R interval in msec. Curve 1 shows the increase in P–R interval during the first period in which the heart was driven electrically. Curve 2 shows the increase in the P–R interval in the second and third periods in which the heart was driven electrically. Curve 3 shows the increase in the presence of neostigmine $0{\cdot}6 \times 10^{-6}$ molar. Curve 4 shows the increase in the presence of neostigmine $1{\cdot}8 \times 10^{-6}$ molar. Curve 5 shows the increase after the injection of 2 mg. atropine.

fibrillation (Fig. 7e) which changed through auricular flutter (Fig. 7f) to a slow auricular rhythm at the rate of 95 per min. (Fig. 7g). Ventricular complexes then began (Fig. 7h), and a 2 : 1 rhythm was established (Fig. 7i). Normal rhythm finally returned at a rate of 118 per min. (Fig. 7j).

Production of Auricular Fibrillation. We have already shown that when acetylcholine is infused at a constant rate into the blood reaching the heart, and electrical stimulation is applied, auricular fibrillation occurs (Burn *et al.*, 1955*a*). We were therefore anxious to know whether auricular fibrillation could be produced by stimulation in the presence of an inhibitor of cholinesterase. For this purpose we used higher concentrations of an inhibitor than for the previous observations, and in order to avoid the atropine-like action that higher concentrations of some inhibitors possess, we chose paraoxon. Results of three experiments are given in Table VII, in each of which fibrillation was produced with three concentrations of paraoxon, the last column showing the period for which fibrillation continued after the stimulation was stopped. When auricular fibrillation was produced by electrical stimulation during the infusion of acetylcholine, the fibrillation continued after stimulation stopped for so long as the acetylcholine was infused. In the experiments with paraoxon fibrillation was only temporary; when stimulation was stopped it continued for some time and then stopped spontaneously. The length of time was, however, greater when the concentration of paraoxon was greater. In two experiments fibrillation occurred during stimulation in the presence of eserine. In Experiment 2 the concentration of eserine was 2×10^{-6}M and the rate of stimulation was 570 per min. In Experiment 8, the concentration of eserine was 5×10^{-5}M and the rate of stimulation was 560 per min. In both experiments fibrillation stopped within a few seconds when stimulation was stopped.

Thus auricular fibrillation was produced by a high rate of stimulation in the presence of three different concentrations of paraoxon in each of three experiments. However, the conditions for the appearance of fibrillation appeared to change slightly in the course of a few minutes. In Fig. 8a fibrillation had been induced and continued when stimulation stopped. The normal rhythm returned as seen in Fig. 8b, and stimulation was begun again at the same rate as before; after 9 stimuli there was complete A-V block with absence of ventricular activity, but the auricles followed each stimulus and did not fibrillate again. In Fig. 8c ventricular complexes returned. In another experiment the reverse happened. The auricles responded to every stimulus up to 1256 per min., but when stimulation was stopped, and then turned on again after 2 minutes, auricular fibrillation began at once.

Fibrillation with Eserine and Acetylcholine. In the previous work in which it was shown that stimulation during the infusion of acetylcholine at constant rate caused auricular fibrillation, the amounts of acetylcholine required varied from 40 μg. per min. to 3·2 mg. per min. We therefore determined the amount of

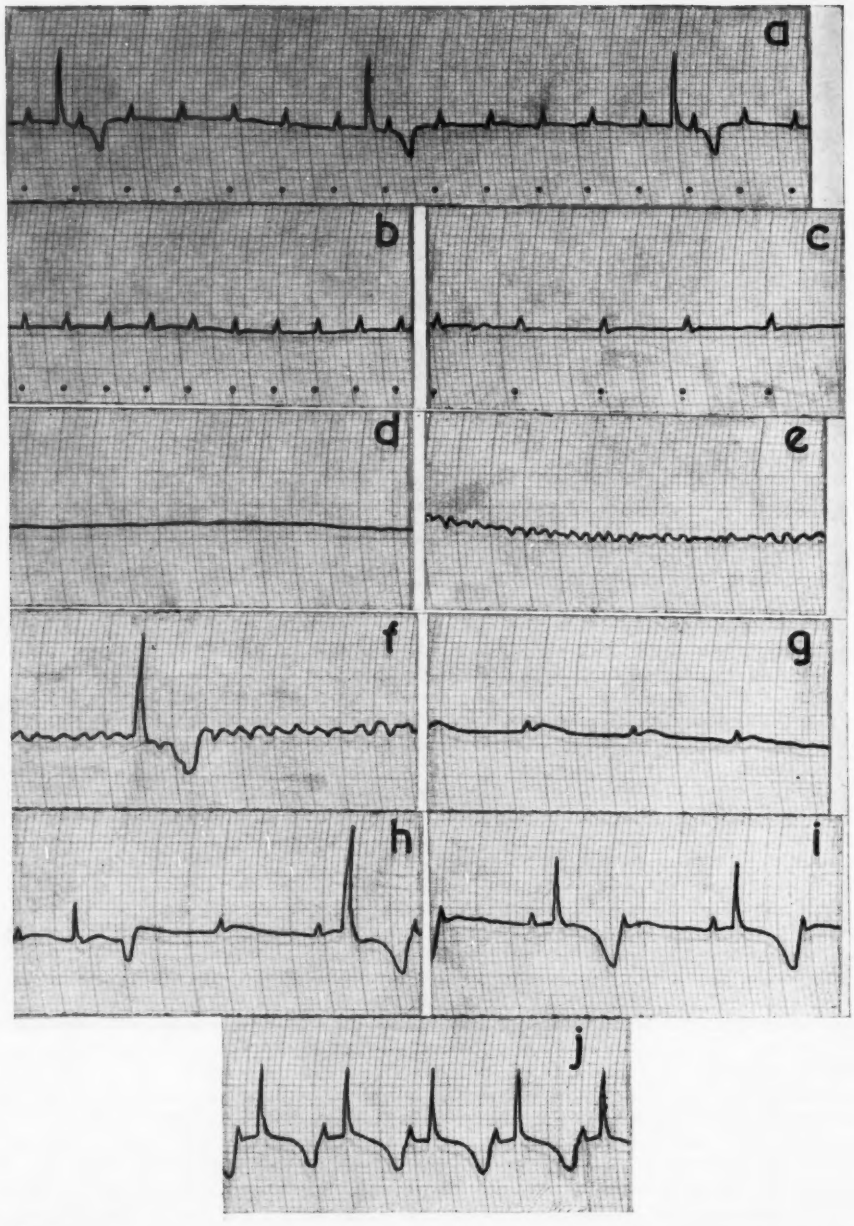

FIG. 7.—Cardiogram of heart–lung preparation. The stimuli are marked by dots. (a) Shows the 6 : 1 block in the presence of neostigmine $1{\cdot}8 \times 10^{-6}$ molar when the rate of stimulation was 198 per min.; (b) shows complete block with absence of ventricular activity when the rate of stimulation was raised to 243 per min.; (c) shows the persistence of this block when the rate was decreased to 120 per min.; (d) shows complete arrest of the heart when the stimulus was stopped. 20 μg atropine was then injected into the left ventricle, and the ventricles were squeezed two or three times to expel the blood; (e) shows auricular fibrillation; (f) shows fibrillation becoming more like flutter; (g) shows a spontaneous auricular rhythm; (h) shows the beginning of ventricular spikes; (i) shows a rhythm with 2 : 1 block; (j) shows a normal rhythm.

TABLE VII

PRODUCTION OF FIBRILLATION

Experiment	Inhibitor	Molar concentration	Rate of stimulation per min.	Duration of fibrillation when stimulus stopped
17	Paraoxon	9×10^{-6}	556	1 min.
	,,	$1{\cdot}8 \times 10^{-5}$	556	3·3 min.
	,,	$3{\cdot}6 \times 10^{-5}$	562	9·6 min.
18	Paraoxon	9×10^{-6}	330	5 min.
	,,	$2{\cdot}7 \times 10^{-5}$	750	25 min.
	,,	10^{-4}	1256	(Stopped by atropine)
19	Paraoxon	9×10^{-6}	708	(Flutter 10 sec.)
	,,	$2{\cdot}7 \times 10^{-5}$	875	1 min.
	,,	$6{\cdot}3 \times 10^{-5}$	865	10 min.

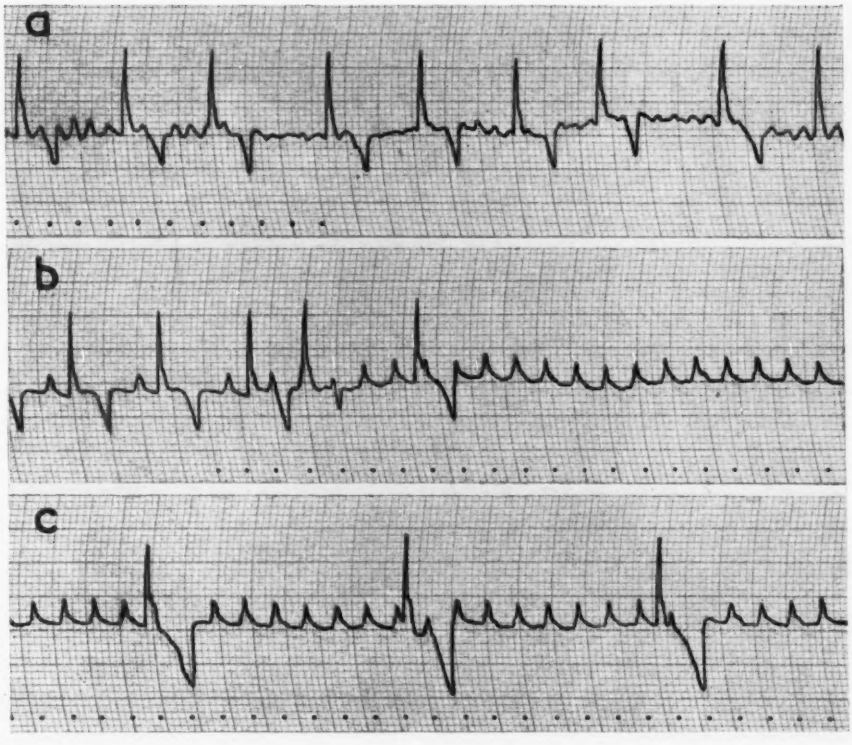

FIG. 8.—Cardiogram of heart–lung preparation. (a) Shows a mixture of auricular flutter and fibrillation in the presence of paraoxon (9×10^{-6} molar) during stimulation at 330 per min. The stimuli are marked by the dots. This continued for 5 min. after cessation of the stimulation. (b) Shows the restored normal rhythm and the complete block produced by resuming the same rate of stimulation; (c) shows the persistence of the block, the ventricular waves being unrelated to the auricular waves.

acetylcholine required in two experiments in which eserine was added to the blood before infusion with acetylcholine began.

In Experiment 2 the amount of eserine added was 0·75 mg. to 1 litre of blood, so that the concentration was 2×10^{-6}M, and infusion of acetylcholine began at 3·5 μg. per min. Fibrillation was seen when the rate of stimulation was 190 per min. and continued when the stimulation was stopped (see Fig. 9a). After 5 minutes the acetylcholine infusion was reduced to 2 μg. per min., and after 4 minutes more it was reduced to 1 μg. per min. After 6 minutes more fibrillation continued and the infusion of acetylcholine was stopped. After one minute fibrillation changed to flutter (Fig. 9b), and then there was a return to normal rhythm (Fig. 9c). In Experiment 1, in the presence of the same amount of eserine, fibrillation continued for 25 min. during the infusion of acetylcholine at the rate of 3·25 μg. per min. These results showed that in the presence of a low concentration of eserine, very small amounts of acetylcholine maintained fibrillation once it had begun.

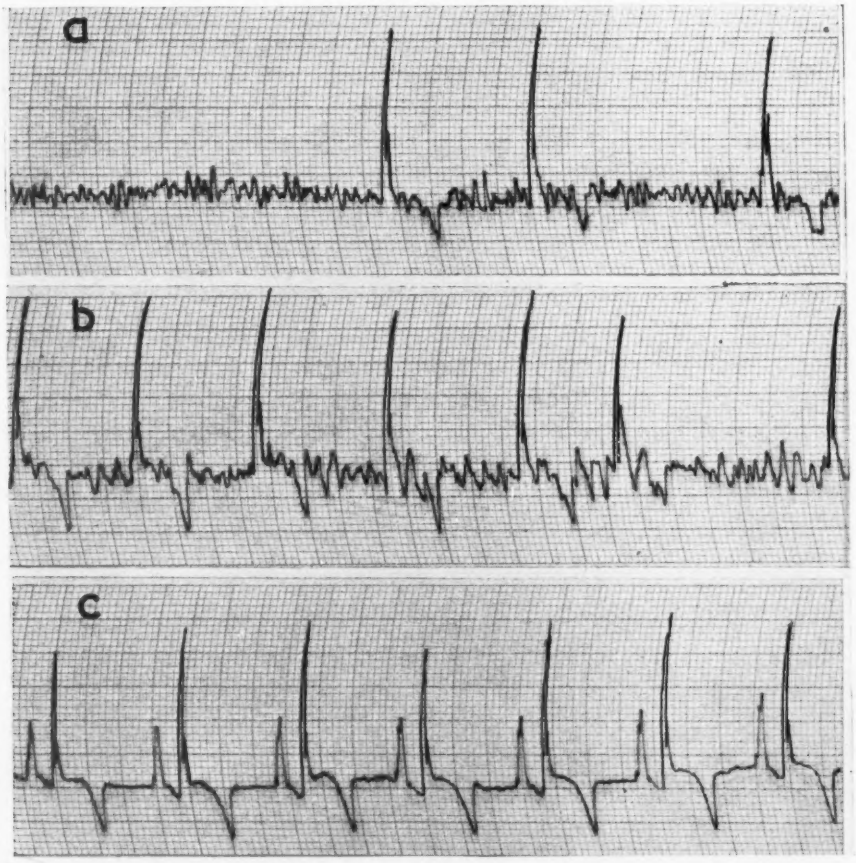

FIG. 9.—Cardiogram of heart–lung preparation. (a) Shows auricular fibrillation produced by stimulation at 190 per min. in the presence of eserine 2×10^{-6} molar and during the infusion of acetylcholine at 3·5 μg. per min. The stimulation was stopped, but the fibrillation persisted so long as the infusion of acetylcholine continued. (b) Shows that after the infusion of acetylcholine was stopped, the fibrillation became more like flutter, and the number of ventricular complexes increased. (c) Shows the return to normal rhythm.

Discussion

When acetylcholine is infused at constant rate into the blood of a heart–lung preparation, the pacemaker is slowed, the P–R interval is prolonged, and the output is observed to decline when the rate is kept constant by electrical stimulation. When the auricles are stimulated electrically at increasing rates, the infusion of acetylcholine lowers the rate of stimulation at which the ventricles cease to respond to every impulse arriving from the auricles. Finally, when the amount of acetylcholine infused per min. is sufficiently high (though for some preparations this amount is not great) electrical stimulation leads to the onset of auricular fibrillation.

The observations that have now been described show that the addition of any one of a number of inhibitors of cholinesterase to the blood has in general the same effects, and that these effects are abolished by atropine. The inference is that acetylcholine is being liberated in the heart–lung preparation, although the vagus nerves are cut, and no stimulation is being applied to them. This liberation of acetylcholine might be from the heart or from the lungs. However, the observations also show that when the heart is driven electrically in the absence of any cholinesterase inhibitor, at the end of the period of stimulation there is a slowing of the pacemaker, a prolongation of the P–R interval, and a diminution of the output, all three changes diminishing in the course of a few minutes. Thus the electrical stimulation appears to cause an increase of a substance in the blood that has the properties of acetylcholine and like it is rapidly destroyed. These observations point to the heart as the source of the acetylcholine that is liberated rather than to the lungs. This evidence is supported by the finding mentioned earlier that the isolated rabbit heart beating spontaneously liberates a substance that in pharmacological tests on other tissues behaves like acetylcholine.

The question then arises from where in the heart is the acetylcholine liberated? During electrical stimulation of the auricles the acetylcholine might be supposed to come from the vagus nerve endings, which might be stimulated directly by the current applied to the auricles. Each shock was, however, only 1 mA in strength and of 0·9 msec. duration, and was applied to the tip of the right auricle. It is unlikely that so mild a stimulus was able to do more than set up a propagated disturbance or that it stimulated other vagal endings than those immediately beneath the electrodes since the nerves in the auricle do not form a syncytium. Electrical stimulation of vagal nerve endings could not in any case account for the effects of inhibitors of cholinesterase on spontaneous rates and on conduction that were seen when no stimulation was applied. Hence the possibility arises that the acetylcholine might come from some non-nervous source. Recently Bülbring *et al.* (1953) have found that the rhythmic movements of the cilia on the gill plates of *Mytilus edulis* are controlled by acetylcholine formed locally in tissue that contains no nervous elements, and as long ago as 1924 Gray drew attention to the close similarity in the responses of these same cilia and of those of the sinus region of the frog heart to a wide variety of changes.

While the effect of adding inhibitors of cholinesterase to the blood in the heart–lung preparation was in general similar to that of infusing acetylcholine, there were points of difference. The effect of inhibitors of cholinesterase in slowing the pacemaker and in lowering the rate at which A-V conduction began to be interrupted was much greater than that of infusions of acetylcholine even when the amounts infused were large. These differences suggested that acetylcholine produced within the heart had readier access to the pacemaker and to the A-V bundle than that coming in the blood stream. There was also the difference that when auricular fibrillation was produced by stimulation during infusion of acetylcholine, it persisted after the stimulation stopped for so long as the acetylcholine was infused; on the other hand, when fibrillation was produced by stimulation in the presence of a cholinesterase inhibitor, it stopped soon after the stimulation stopped. This fact, taken in conjunction with the observation that the time fibrillation then lasted was greater in proportion to the amount of cholinesterase inhibitor present, suggests that the fibrillation was due to the acetylcholine liberated by driving the heart at high rates. It is thus possible that the observation made by Rothberger and Winterberg (1910) that driving the heart at high rates leads to

auricular fibrillation is explained by the acetylcholine so produced. In our previous paper we suggested that production of fibrillation in this way was due to the use of electrodes that produced trauma. We believe that trauma introduces another factor, but we have recently observed the production of flutter persisting for a few minutes after withdrawal of the stimulus when using electrodes that caused minimal trauma. However, such flutter is exceptional and brief; as a rule the acetylcholine formed is destroyed too quickly.

The observations described in this paper represent additional evidence that the beating heart liberates acetylcholine and that the amount liberated is increased when the rate of beating rises. That which is liberated when no stimulation is applied to the vagus nerve or to the heart itself may be certainly described as intrinsic. To judge from the evidence that the activity of the isolated auricles of the rabbit varies with the power of the auricular tissue to synthesize acetylcholine, it would appear that the intrinsic formation is of great importance for the cardiac mechanism, and that this formation may constitute the building up of the excitement which leads to each contraction. Thus it may play a part in cardiac muscle somewhat analogous to the part it plays in skeletal muscle where its arrival at the motor end plate causes a flow of current that leads to a propagated disturbance. Or its role may be to facilitate the development of such a disturbance in response to some other more basic processes.

It is certain that both acetylcholine and cholinesterase inhibitors can exaggerate processes that are part of the normal cardiac function, as is illustrated by the effect of inhibitors of cholinesterase in lowering the rate of stimulation at which A-V block begins. This effect is abolished by atropine, but block still occurs though only at a higher auricular rate. Thus the production of block is possible when the action of acetylcholine is excluded by atropine. However, in the absence of atropine block is greatly facilitated by acetylcholine.

The results obtained in this and the preceding paper (Burn *et al.*, 1955*a*) are perhaps of clinical interest concerning the cause of auricular fibrillation. We have produced this regularly by stimulating the auricle in the heart–lung preparation either during the infusion of acetylcholine or after the addition of an inhibitor of cholinesterase to the blood. The stimulation necessary during the infusion of acetylcholine was no more than two or three shocks in some experiments, and the results suggested that auricular fibrillation might be expected to arise in man when an ectopic focus began to discharge impulses during a period of continued high vagal tone, or during a period in which much acetylcholine was produced by the heart itself due to a high spontaneous rate.

Summary

When eserine (physostigmine) or neostigmine (prostigmin) is injected into the normal circulation, the heart rate is slowed. This action is considered equivalent to increased vagal action, since it is explained by a lessened rate of destruction of the acetycholine that is liberated by vagal stimulation. The experiments now described have been carried out in the heart–lung preparation of the dog in which the vagi are cut. When physostigmine or prostigmin was added to the blood it produced effects similar to those produced by acetylcholine, namely, slowing of the heart rate, prolongation of the P–R interval, and reduction of the output; these effects were abolished by atropine. Thus it appeared that in the heart–lung preparation, acetylcholine was being liberated from some point other than the vagal nerve endings.

When the heart was driven electrically by stimulation applied to the right auricle, it was found that when stimulation stopped, the spontaneous rate was less than before the stimulation began; also the P–R interval was prolonged and the output was reduced. In a few minutes the initial values were restored. Thus it appeared that electrical stimulation of the heart caused the appearance of acetycholine in the blood, this acetylcholine being destroyed in a few minutes.

When the heart was driven electrically at increasing rates a critical point was reached at which the ventricular rate fell below the auricular rate (partial block), and at higher rates of stimulation the ventricular fell to half the auricular rate (2 : 1 block). In the presence of eserine or other inhibitors of cholinesterase the critical rate of stimulation for the commencement of block was much

lower; the rate at which the 2 : 1 rhythm occurred was also much lower. When atropine was added these changes were reversed.

When the heart was driven electrically at increasing rates in the presence of higher concentrations of eserine or other inhibitors of cholinesterase, auricular fibrillation was produced. When the stimulation was stopped the fibrillation continued for a short time, the length of time being greater according to the concentration of inhibitor that was present. We have shown previously that, when acetylcholine is infused and the heart is stimulated electrically, auricular fibrillation is produced. The present evidence therefore suggests that acetylcholine set free in the heart and preserved by an inhibitor of cholinesterase can also cause auricular fibrillation when the heart is stimulated electrically.

We wish to thank Mr. H. W. Ling for his invaluable help in the experiments. One of us (J.H.B.) is indebted to the Royal Society for a grant to purchase the Cossor electrocardiograph. We also wish to thank Sir Charles Lovatt Evans for a supply of Paraoxon, Dr. D. W. Adamson for a supply of BW.284C.51, and the Hoffmann-la-Roche Co. for a supply of Nu 683.

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RUPTURE OF THE INTERVENTRICULAR SEPTUM

BY

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Rupture of the interventricular septum is an uncommon complication of cardiac infarction. The seven cases reported here illustrate the clinical and pathological features of this condition.

In 1948, Fowler and Failey, in a survey of previously reported cases, found records of 60 patients who had myocardial infarction involving the interventricular septum with subsequent septal rupture; in 17 of these the condition was recognized clinically. Physicians are now becoming increasingly aware of this complication of cardiac infarction and in recent years a number of isolated case reports have appeared (Leonard and Daniels, 1938; Nareff *et al.*, 1950; Black, 1952; Evans and Anderson, 1952; Hamilton *et al.*, 1954; Arons and O'Rourke, 1954.)

The following seven instances of septal rupture occurred in patients admitted to the Royal Victoria Hospital, Belfast, and to the Belfast City Hospital. In the case of patients not seen personally by one of us, clinical and pathological records were made available by the physicians and pathologists concerned. The clinical and pathological features of all seven cases are summarized in tabular form, and those of one case are presented in some detail.

TABLE I

THE CLINICAL FEATURES OF SEVEN CASES OF RUPTURED INTERVENTRICULAR SEPTUM

	Age	Blood pressure (m.m/Hg).	Auscultation	Thrill	Cardiac rhythm	Pallor	Hb (g.%.)	Cyanosis	Peripheral œdema
Case 1	56	115/105	Loud systolic murmur maximal in fourth left intercostal space	Present	Regular	++	14·1	++	
Case 2	75	190/130	Systolic murmur heard over præcordium		Regular			++	Absent
Case 3	74	90/?	Loud systolic murmur all over præcordium		Fibrillation 150/min.	++	12·7		
Case 4	50	130/100	Harsh systolic and diastolic murmurs between apex beat and sternum			++	11·2	++	
Case 5	75	120/80	Heart sounds faint and almost inaudible		Gailop rhythm	++		++	Gross
Case 6	87	130/80	Loud blowing systolic murmur maximal to left of sternum	Present		++	6·4		
Case 7	74	135/90	Mitral systolic and diastolic murmurs			++			Gross

TABLE II

THE POST-MORTEM FINDINGS IN SEVEN CASES OF RUPTURED INTERVENTRICULAR SEPTUM

	Heart weight (g.)	Occlusion	Area infarcted	Site of rupture	Œdema lungs	Liver weight (g.)	Central zonal necrosis
Case 1 (male)	550	Anterior descending branch left coronary artery	Antero-septal region	Below centre of anterior septal margin	Acute œdema present	1600	Present
Case 2 (male)	500	Anterior descending branch left coronary artery	Septum extending to posterior wall left ventricle	Posterior apical part of septum	Moderate œdema	1600	Present
Case 3 (female)	560	No satisfactory occlusion found. Gross atheroma present	Antero-septal region	Lower apical part of septum	Chronic venous congestion	1500	Present
Case 4 (male)	500	Anterior descending branch left coronary artery	Antero-septal region	Lower apical part of septum	Gross œdema	2400	Present
Case 5 (female)	480	Anterior descending branch left coronary artery	Antero-septal region	Lower apical part of septum	Acute œdema	1400	Present
Case 6 (male)	400	Atheroma and calcification left coronary. Right coronary abnormally small	Lower half of septum	One inch above apex in septum	Œdema with terminal pneumonia	900	Central zonal congestion
Case 7 (female)	350	Gross atheroma. Hæmorrhage into plaque in left anterior descending coronary	Anterior wall left ventricle and apical portion of septum	Apical part of septum	Acute œdema	1600	Central zonal congestion

CASE REPORT

G. McK., a 56-year-old man, was admitted to hospital with a diagnosis of internal hæmorrhage. On examination he was seen to be shocked and cyanosed. His conjunctivæ were blanched to such an extent as to suggest profound anæmia. The hæmoglobin was 99 per cent (14·1 g./100 ml.). The cardiac rhythm was regular, the pulse volume poor, and there was gross jugular venous congestion. The blood pressure was not recordable. A loud systolic murmur was maximal in the fourth left intercostal space just to the left of the sternum. Pulmonary œdema was present and the liver was considerably enlarged. There were 15,000 leucocytes/cu. mm. A chest X-ray showed moderate cardiac enlargement and pulmonary congestion. An electrocardiogram showed a typical antero-septal left ventricular infarct (Fig. 1). The blood urea was 147 mg. per 100 ml. Four days later, the patient became disorientated and increasingly cyanosed, and icterus was noted. A further electrocardiogram revealed no extension of the infarction. He lapsed into coma and his condition deteriorated further. Three days later he died. The records of this patient revealed that he had been treated for hypertension several years previously at which time his blood pressure was 240/140 and an electrocardiogram showed only hypertensive changes. His heart sounds at that time were normal.

Post-mortem Findings. The body was icteric. There was a fibrinous pericarditis with an adhesion on the anterior surface of the left ventricle (Fig. 2). The heart weighed 550 g. There was ante-mortem

thrombus in the appendage of the dilated right atrium. The right ventricle had an opening in the antero-superior part of the septal wall, with surrounding discoloured and hæmorrhagic myocardium. The left atrium was normal. The left ventricle was dilated, especially in the septal region where the dilatation was aneurysmal. It was here that perforation had occurred. The apical third of the septum, the anterior wall of the left ventricle and a small portion of the posterior wall at the apex were discoloured and thin. Apical

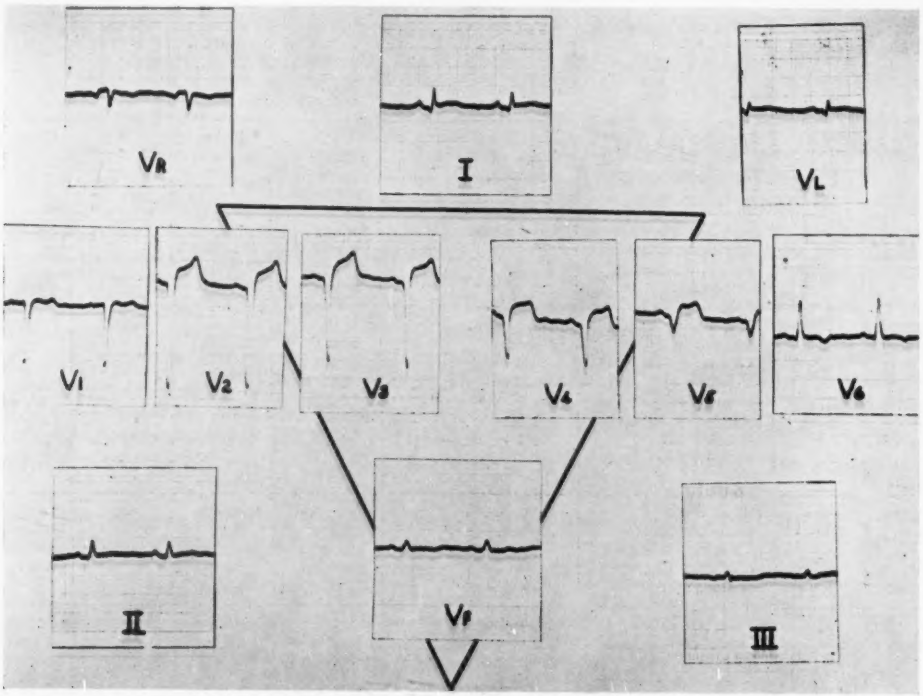

FIG. 1.—Electrocardiogram showing typical features of antero-septal infarction of the left ventricle.

endocardial thrombi were present. The anterior descending branch of the left coronary artery contained a thrombotic occlusion near its origin.

Histologically the infarcted areas showed extensive necrosis of the myocardium. In some parts the entire thickness of the ventricle was involved with the exception of a narrow surviving epicardial zone. The coronaries were markedly atheromatous and the presence of a recent thrombotic occlusion was confirmed. There was acute pulmonary œdema, macroscopically and histologically.

The liver weighed 1600 g. and had a " nutmeg " pattern. Histologically the liver showed intense central zonal congestion and necrosis (Fig. 3).

DISCUSSION

Sager (1934) found that only 3 per cent of myocardial ruptures occurred through the interventricular septum. This infrequency of septal rupture has been ascribed by Gross (1921) to its rich anastomotic blood supply. Most authors agree that septal rupture is found in the presence of severe coronary arteriosclerosis. However, an assessment of this problem must include consideration of other factors. The splinting effect of the right ventricular pressure in reducing the pressure gradient across the septum tends to reduce the incidence of interventricular septal rupture.

FIG. 2.—Left heart showing the infarcted area, septal perforation, pericardial adhesions and mural thrombus.

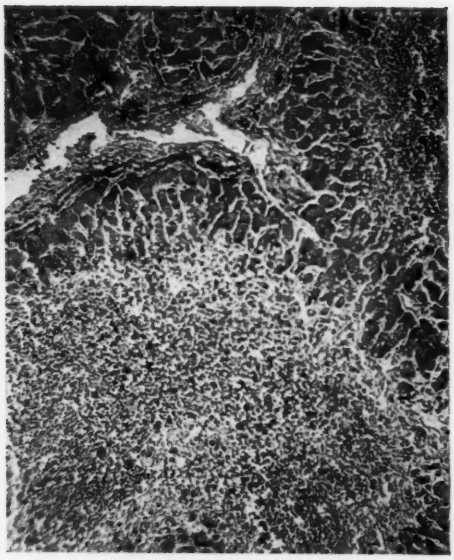

FIG. 3.—Microscopical appearances of liver showing central zonal necrosis (×100, H. & E.)

On the other hand, if hypertension persists after the occurrence of septal or non-septal infarction, ventricular rupture is more likely to result (Edmondson and Hoxie, 1942).

The following factors appear to contribute to this complication of cardiac infarction.

(1) Complete or almost complete infarction of the full thickness of the septal muscle.

(2) The time factor. Most septal ruptures occur between the third and twelfth days after infarction. Edmondson and Hoxie (1942) found the average survival period to be 7·4 days.

(3) Age. The average age of the patients in this series was 70 years.

(4) Hypertension. This is difficult to assess clinically because many of these patients are admitted for the first time after the occurrence of infarction with a consequent fall in blood pressure. The heart weight provides an index of the degree of cardiac hypertrophy present at death. In this series the average heart weight was above 475 g.

The pathological effects of septal rupture are of considerable interest. Intense vascular congestion of the liver lobules occurs and in five of our cases it was associated with central zonal necrosis of the liver lobules (Fig. 3). In our first case the degree of liver damage was such as to result in obvious jaundice. The septal rupture is usually small. Sager (1934) commented on the fact that the præcordial murmur is often loud, despite the patient's poor general condition and that it is usually maximal to the left of the lower end of the sternum.

Nareff *et al.* (1950) stated that it might be confused with that of aortic stenosis, mitral insufficiency, or rupture of chordæ tendineæ or papillary muscles. Fowler and Failey (1948), discussing

rupture of a papillary muscle, state that this complication is to be suspected when the condition of the patient suddenly becomes worse, the murmurs become louder and nearer the apex, and the ensuing heart failure is left-sided rather than right-sided. They considered that rupture of chordæ tendineæ was more likely in middle-aged or elderly patients who, suddenly, without dramatic incident, develop a loud systolic murmur, usually with a thrill, maximal at the cardiac apex and along the left sternal border. Congestive heart failure in these cases does not usually develop for months or years.

Rupture usually occurs in the apical end of the septum near one or other wall of the ventricle. This was held by Nareff *et al.* (1950) to account for the rarity of intraventricular conduction defects. They mention that rupture is often associated with a dramatic deterioration in the patient's general condition with peripheral circulatory failure and the rather abrupt appearance of signs of right ventricular failure. In our experience, the shock and peripheral circulatory failure following septal rupture have been so marked as to lead to an erroneous clinical impression of anæmia on several occasions.

It would appear that septal rupture is more likely to occur in the elderly hypertensive patient with advanced coronary arteriosclerosis, who has suffered cardiac infarction during the previous fortnight. The prognosis seems to be uniformly poor. All the patients in this series died within a few weeks of septal rupture.

Summary

The clinical and pathological findings in seven patients who had cardiac infarction involving the interventricular septum with consequent septal rupture are presented.

The causation and clinical features of this unusual complication of cardiac infarction are discussed. Suggestive clinical signs are the appearance of a loud præcordial systolic murmur, maximal to the left of the sternum in the fourth intercostal space, and often an associated systolic thrill in this area. At the time of septal rupture the patient's condition deteriorates conspicuously; there is usually profound shock, with peripheral circulatory failure and right heart failure.

We are indebted to Professor Biggart and Professor Bull for their ready advice during the preparation of this paper. We wish to thank Professor Biggart, Dr. Robert Marshall, Dr. T. H. Crozier, Dr. T. A. Kean and Dr. George Adams for permission to publish details of these patients, and Mr. David Mehaffey, A.R.P.S., for the photography.

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RECORDINGS OF PRESSURE OBTAINED DURING CATHETERIZATION OF THE GREAT CARDIAC VEIN

BY

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The introduction of the cardiac catheter into the coronary sinus in man has been described by several authors (Bing *et al.*, 1947; Bing *et al.*, 1949; Culbertson *et al.*, 1949; Soulié, Carlotti *et al.*, 1949; Soulié, Servelle *et al.*, 1949; McMichael and Mounsey, 1951; Smith *et al.*, 1951; Miller *et al.*, 1953). Usually, the pressure recorded in the coronary sinus has not been found to differ materially from that in the right atrium. However, in one of the cases reported by Bing *et al.* (1949), where the catheter had been pushed far into the sinus to obstruct the great cardiac vein, a pronounced pulse wave was found with a peak of 45–50 mm. Hg " which closely followed the left ventricular ejection period." In one of the cases described by Culbertson *et al.* (1949) a pulse wave was also recorded deep in the coronary sinus which was at first mistaken for a right ventricular recording, and a similar instance is reported by Soulié *et al.* (1949*a*) when the pulse wave had some resemblance to a tracing from the pulmonary artery. Recently, Miller *et al.* (1953) have described several cases in which a prominent pulse wave was recorded when the catheter was inserted far into the coronary sinus. In our records there are nine manometric tracings taken when the catheter had been inadvertently introduced into this position. The following is a description and discussion of these tracings.

Materials and Methods

The recordings were taken during the routine cardiac catheterization of patients, all of whom had abnormal hearts. The abnormalities were as follows.

Case A: Pulmonary valvular stenosis.
Case B: Atrial septal defect with possibly pulmonary valvular stenosis.
Case C: Atrial septal defect with severe pulmonary hypertension.
Case D: Pulmonary infundibular stenosis with patent ductus arteriosus.
Case E: Primary pulmonary hypertension with pulmonary incompetence.
Case F: Mitral stenosis.
Case G: Pulmonary valvular stenosis.
Case H: Mitral stenosis.

All the patients had hypertrophy of the right ventricle and a high right ventricular systolic pressure (Table I). They were all adults.

Cournand catheters were introduced under local anæsthesia. A Size 7F catheter was used in all cases except for one occasion when an 8F catheter was employed. Recordings of pressure were taken by means of a capacitance manometer with simultaneous electrocardiogram, using the apparatus devised by Bareham (1954). Zero was taken at the level of the table on which the patient lay. The oxygen uptake of samples of blood was measured by means of the Haldane method (Haldane, 1920). The oxygen capacity of the blood was assessed from the hæmoglobin estimation.

* Wiltshire Memorial Research Scholar.

TABLE I

PRESSURES RECORDED IN GREAT CARDIAC VEIN AND RIGHT VENTRICLE DURING CARDIAC CATHETERIZATION

	Case A		Case B		Case C, 1953		Case C, 1954	
	G.C.V.	R.V.	G.C.V.	R.V.	G.C.V.	R.V.	G.C.V.	R.V.
Interval between start of QRS and start of pulse wave (sec.)	0·08	0·08	0·08	0·00	0·04	0·08	0·12	0·12
Duration of pulse wave (sec.)	0·46	0·50	0·42	0·42	0·48	0·58	0·48	0·54
Height of pulse wave (mm. Hg) ..	50	115	68	100	40	170	25	150
Length of cardiac cycle (sec.) ..	1·02	0·92	0·78	0·76	1·00	1·02	0·86	1·00

	Case D		Case E		Case F		Case G	
	G.C.V.	R.V.	G.C.V.	R.V.	G.C.V.	R.V.	G.C.V.	R.V.
Interval between start of QRS and start of pulse wave (sec.)	0·00	0·04	0·00	0·06	0·16	0·06	0·08	0·08
Duration of pulse wave (sec.)	0·40	0·40	0·48	0·40	0·40	0·48	0·42	0·44
Height of pulse wave (mm. Hg) ..	30	77	30	85	40	100	46	92
Length of cardiac cycle (sec.) ..	0·78	0·70	0·76	0·76	0·58	0·78	0·82	0·82

G.C.V.=occluded great cardiac vein. R.V.=right ventricle.

In every instance the catheter had been advanced along the coronary sinus as far as it would go, as judged by the resistance to the operator's hand and the kinking of the free length of catheter in the right atrium. In each case, the nearness of the tip of the catheter to the left border of the heart shadow in the antero-posterior view led us to believe that it actually lay in the great cardiac vein (Fig. 1). Often the catheter could be seen to pass for some distance anteriorly round the left border

TABLE II

OXYGEN CONTENT AND SATURATION OF BLOOD SAMPLES FROM GREAT CARDIAC VEIN AND CHAMBERS OF RIGHT HEART

Case	Oxygen content (vols. per 100 ml.)			Oxygen saturation (percentage)		
	Great cardiac vein	Right ventricle	Right atrium	Great cardiac vein	Right ventricle	Right atrium
A	5·6	14·0	15·4	28	70	77
B	6·2	17·9	17·6	31	91	89
C 1953 ..	7·6	19·2	20·7	30	76	81
C 1954 ..	4·1	14·8	14·9	19	67	67
D	6·7	13·1	12·7	40	78	75
E	9·2	19·9	17·9	41	80	80
F	5·8	13·7	14·5	30	71	75
G	7·9	14·0	14·2	40	70	71
H	5·8	—	9·1	30	—	47

of the heart. The catheter can not always be introduced as far into the coronary sinus system as occurred in these cases and presumably the valve of Vieussens will often prevent its passage into the great cardiac vein.

RESULTS

No discomfort or mishap occurred in any of the patients during or after the time that the catheter lay in the coronary sinus, nor was there any change in the electrocardiogram. Samples of blood could be withdrawn freely from the catheter when it was wedged in the great cardiac vein and all had a very low oxygen content (Table II).

In the first seven patients, a distinct systolic pulse wave was recorded. The dimensions of this

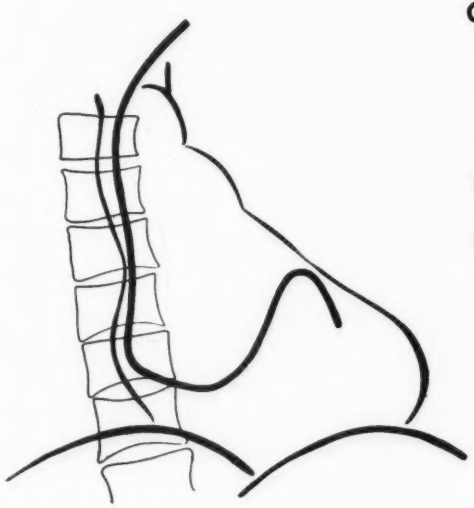


FIG. 1.—Drawing from X-ray plate to show position of catheter in Case A.

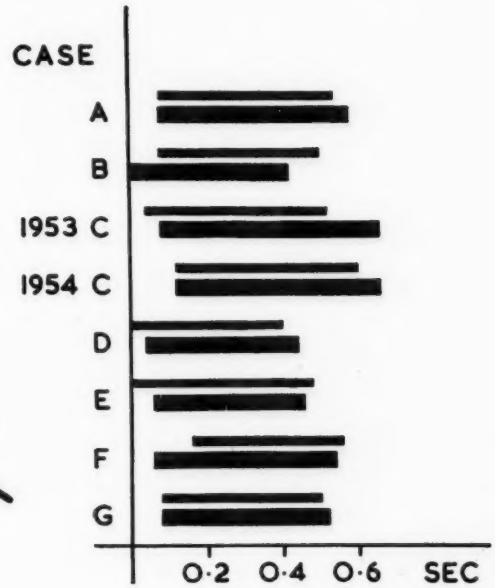


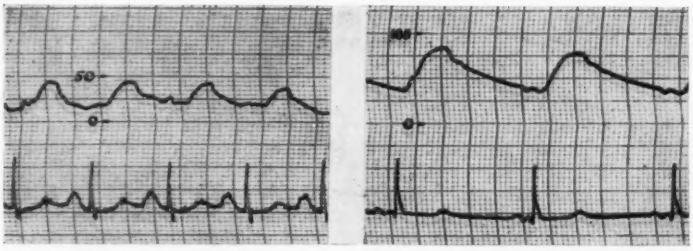
FIG. 2.—Diagram to compare the timing of the pulse wave in the occluded great cardiac vein (thin, upper lines) and right ventricle (thick, lower lines) in each patient. The vertical line represents the start of the QRS complex of a simultaneous electrocardiogram.

wave and its position in the cardiac cycle are given in Table I where they are compared with similar figures for the systolic pulse wave in the right ventricle. The recordings from these two sites were not simultaneous and the heart rate was, therefore, different in each tracing. Nevertheless, in six of these cases, the timing of the systolic pulse wave in the great cardiac vein is seen to coincide approximately with that in the right ventricle (Fig. 2). In Case F, the wave in the great cardiac vein starts considerably later than that in the right ventricle, but they both end at approximately the same point (Fig. 2 and 3).

The shape of the pulse wave varied. In Cases A, B, and G it simulated the contour of a right ventricular pulse wave (Harris, 1955) although in all these instances it differed from the shape of

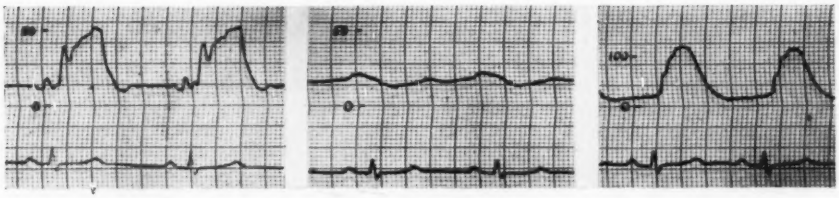
the right ventricular systolic wave itself (Fig. 4 and 5). In Case F, the appearance of the pulse wave in the occluded great cardiac vein mimicked the form of wave normally found in the pulmonary artery (Fig. 3). In Cases C, D, and E, the wave was less specific (Fig. 6). Patient C was catheterized a year later and the two recordings from the great cardiac vein are very similar (Fig. 6). Occasionally the main pressure wave was preceded by a small wave that seemed to coincide with auricular systole.

The height of the pulse wave ranged between 25 and 68 mm. Hg. In every instance it was lower than the systolic pressure in the right ventricle. In all cases, however, the right ventricular systolic pressure was abnormally high.



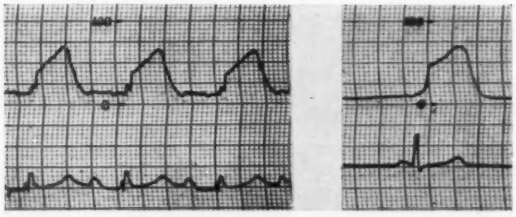
A B

FIG. 3.—Recordings from (A) occluded great cardiac vein and (B) main pulmonary artery in Case F.



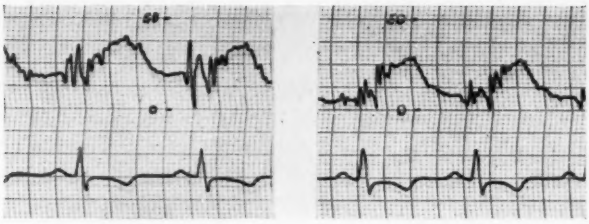
A B C

FIG. 4.—Recordings from (A) occluded great cardiac vein, (B) right atrium, and (C) right ventricle in Case A.



A B

FIG. 5.—(A) Recording from the occluded great cardiac vein in Case B. (B) Recording from the right ventricle of a patient with mitral stenosis. The tracings are compared in order to show how closely the recording from the great cardiac vein can simulate a right ventricular tracing.



1953 1954

FIG. 6.—Recordings from the occuluded great cardiac vein taken on two different occasions from Case C.

DISCUSSION

In 6 out of 7 cases, the pulse wave recorded when the catheter was wedged in the great cardiac vein coincided approximately with the systolic wave in the right ventricle (Fig. 2). It seems most likely, therefore, that the rise in pressure in the great cardiac vein was in fact caused by the contraction of the ventricles. The outflow of blood from the coronary sinus of the dog has been shown to occur mainly or entirely during the period of ventricular systole (Anrep *et al.*, 1927; Johnson and Wiggers, 1937). A systolic pulse wave would therefore be expected in the coronary sinus if the flow of blood were obstructed to any degree. The curves of velocity of flow in the coronary sinus described by Anrep *et al.* (1927), and Johnson and Wiggers (1937) reach a peak towards the end of systole, and in our records the peak of the pressure wave also occurred at this point.

Johnson and Wiggers (1937), Katz *et al.* (1938), and Gregg and Shipley (1947) have shown that, under experimental conditions, a rise in right ventricular systolic pressure causes an increase in outflow of blood from the coronary sinus. It so happened that in all the patients described here, there was in fact a high right ventricular systolic pressure. There was, however, no correlation between the height of the pressure wave in the great cardiac vein and the systolic pressure in the right ventricle. Of the ten cases described by Miller *et al.*, the right ventricular pressure was found to be normal in one and was probably normal in one other; seven patients had a raised pressure in the right ventricle.

Johnson and Wiggers (1937) and Katz *et al.* (1938) suggest that a high right ventricular systolic pressure causes a retrograde flow of blood in the Thebesian veins from the cavity of the right ventricle into the coronary sinus. It seems unlikely that this occurred to any substantial extent in our patients, since the samples of blood withdrawn from the great cardiac vein all had the usual low content of oxygen (Table II) (Bing *et al.*, 1949). Most probably, therefore, the pulse wave in the great cardiac vein was due simply to a squeezing of blood from the capillaries and venules of the myocardium during contraction of the ventricles.

The pulse waves deep in the coronary sinus described by Miller *et al.* (1953) occurred a little later in the cardiac cycle and these authors suggest that they were due to a transmission of the pulse wave in the coronary artery across the capillary bed. This explanation was also given by Bing *et al.* (1949). Such a mechanism can certainly occur across the pulmonary capillary bed (Weissel *et al.*, 1952). As far as the coronary circulation is concerned, however, it cannot explain the appearance of a venous pulse wave as early in the cardiac cycle as is shown by most of our tracings.

The pulse wave in the great cardiac vein may resemble a right ventricular tracing not only in its timing but in its shape (Fig. 5) and in its height (Table I). It may, therefore, be impossible to say from the manometric tracing alone that the catheter is not in the right ventricle. This may be an added source of confusion since in the postero-anterior view the catheter will often appear to be in the right ventricle or the main pulmonary artery. The recognition of this fact could be important

in view of the possible dangers attached to deep catheterization of the coronary sinus (McMichael and Mounsey, 1951; Smith *et al.*, 1951).

Summary

In eight patients, a cardiac catheter was passed far into the coronary sinus and was thought to have occluded the great cardiac vein. Manometric recordings at this site revealed a prominent systolic pulse wave in seven patients. This wave coincided approximately with the systolic pulse wave of the right ventricle in six cases and it seems to be caused by ventricular contraction. The pulse wave may simulate closely the appearance of a right ventricular recording and lead to confusion as to the position of the catheter. Samples of blood taken from this position all had an extremely low oxygen content.

We wish to thank Dr. Terence East for his advice and encouragement.

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ELECTROCARDIOGRAPHY IN MITRAL VALVULAR DISEASE

BY

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The introduction of surgical treatment for valvular heart disease demands meticulous attention to detail in all aspects of the assessment. A number of studies have been made on the electrocardiographic changes that occur in patients with rheumatic heart disease and their relationship to clinical and pathological findings but many were before the introduction of multiple chest leads.

We have made an electrocardiographic study of mitral valvular disease in a series of patients subjected to operation and in a series of post-mortem cases in all of whom detailed clinical, radiological, and usually cardiac catheterization studies were available. The opportunity has been taken to review the generally accepted criteria for right ventricular hypertrophy (R.V.H.) in the light of this experience, and the cardiographic changes have been related to the clinical findings, special investigations, and operative findings in order to decide the practical value of electrocardiography in the assessment of patients for valvotomy.

Material and Methods

There were 200 patients in the operation series. Of these, 177 had pure or predominant mitral stenosis and were treated by valvotomy and 23 had predominant mitral incompetence and most of them were treated by valvoplasty. Sixty also had aortic incompetence, 3 aortic stenosis, and 15 essential hypertension (B.P. >160/100) in varying degree. Some had more than one complication.

There were 38 cases in the post-mortem series. Of these 25 had pure or predominant mitral stenosis and 13 had predominant mitral incompetence. Twelve of them had also aortic incompetence, 6 aortic stenosis, and 3 essential hypertension in varying degree. Some had more than one complication.

In addition, we have examined the cardiograms in 2000 consecutive patients (excluding the present series) in whom a full series of leads had been recorded to assist the evaluation of certain abnormal features in the operative and post-mortem series.

Standard and augmented unipolar limb leads, together with præcordial leads V1–V7 and CR1, were taken in all the 200 operation cases and in 36 of the 38 post-mortem cases. Right-sided V leads were also recorded in 141 cases. Each lead was individually standardized to give a deflection of 10 mm. for 1 mv. difference of potential. All records were made with the patient recumbent.

The following points were studied: axis deviation, algebraical sum of R+S in lead I, electrical position of heart; P waves, Q–T and P–R intervals; absolute height of R and of S and the R/S ratio in V1 and V2, CR1, V5 and V6, V3R, V4R and VE; Q waves; height of R and R/Q ratio in aVR; flattening or inversion of T and depression of S–T segment in V1, V2, V5, V6; patterns of right bundle branch block; and ventricular activation time.

Standard Limb Leads

The amount of useful information obtainable from standard limb leads alone is limited. The absence of any cardiographic abnormality suggests that the degree of underlying valvular disease is probably slight

but reliance cannot be placed on this because 9 patients in sinus rhythm with significant mitral disease had normal standard leads apart from minor changes in the P waves. In 21 auricular fibrillation was the only abnormality. Broad or bifid P waves of the type described below are strongly suggestive of mitral disease. Signs of R.V.H. in præcordial leads were present in 11 cases in which there was not even suggestive evidence of this in the standard limb leads. In the past, right axis deviation with negative T waves in standard limb leads II and III was considered the classical pattern of R.V.H. This was present in only 34 of the present series of 115 cases in which R.V.H. was diagnosed electrocardiographically. Myers *et al.* (1948) have emphasized that the pattern does not necessarily signify R.V.H. and that with a vertical heart may occur in normals or even with left ventricular hypertrophy (L.V.H.). Likewise changes due to L.V.H. may be present only in the præcordial leads.

Axis deviation can be calculated and is discussed below. Right axis deviation associated with auricular fibrillation or with bifid P waves of the type described below by itself strongly suggests the presence of mitral stenosis. Finally the presence and nature of an arrhythmia may be confirmed or disclosed.

Axis Deviation

The electrical axis of the heart can be calculated from the standard limb leads with reference to Einthoven's triangle. For convenience we have used the method described by Dieuaide (1921) and recommended by Ashman and Hull (1941). The limitations of axis deviation as a guide to ventricular hypertrophy have long been recognized but nevertheless deviations from the normal range are of clinical value and may serve to indicate the need for recording other leads or in cases of mitral stenosis as a warning that some significant complication is present. The upper limits of normal for axis deviation in adults have been placed at 90° by Burch and Winsor (1949) and at 92° by Ashman and Hull (1941). Both authors refer to rare exceptions. Carouso *et al.* (1951) found that 99 per cent of normal people have an axis of less then 90°. In our series axis deviation was divided into four grades: (1) under 90°=120 cases; (2) 90–99°=35 cases; (3) 100–109°=25 cases; and (4) 110° or over=20 cases. All those in Group 4, 20/25 in Group 3, and 23/35 in Group 2 had signs of R.V.H. in the præcordial leads. Since signs of R.V.H. were present in 89 per cent of cases in which R.A.D.$>$100° this degree of R.A.D. in itself strongly suggests that R.V.H. is present. The converse does not hold because signs of R.V.H. were present in 49 out of 120 (41%) patients with R.A.D.$<$90°. On the other hand there was no close correlation between the degree of R.A.D. and the severity of the R.V.H. pattern.

In the majority of cases the correlation between the degree of R.A.D. as calculated and the algebraical sum of R+S in lead I was close. However, axis deviation is calculated by plotting the algebraical sum of R+S in lead I against the algebraical sum of R+S in lead III. III is an unreliable lead in that it is influenced by body build and in particular by the height of the diaphragm. It sometimes happens that when from examination of lead I considerable R.A.D. can be expected, i.e. by a small or absent R and a significant S, these findings are, so to speak, neutralized by a tall R in lead III.

We, therefore, compared the algebraical sum of R+S in lead I with R.A.D. calculated in the usual manner and correlated this figure, which is simply obtained, with evidence for R.V.H. in the chest leads. In each of 33 cases in which R+S in lead I amounted to −3 mm., in 7 of 11 cases when it was −2 and in 16 of 25 in which it was −1, signs of R.V.H. were present.

It is concluded, therefore, that in patients with mitral stenosis, an algebraical sum of the R and S waves in standard lead I amounting to −3 mm. or less can be taken as strong presumptive evidence for R.V.H.

The Electrical Position of the Heart

The determination of the electrical position of the heart can be made according to the criteria published by Wilson *et al.* (1946) or by Goldberger (1953). However, these authors express their conclusions in different terms and we have found that the cardiograms of some of our patients cannot be fitted into groups described by either of them. Many workers refer to the electrical position of the heart without stating the criteria on which the assessment has been made. Familiarity with the electrical position is necessary for a full understanding of all the various patterns, but in our opinion is not of practical value except in the detection of biventricular hypertrophy and in the elucidation of atypical patterns that might otherwise be misinterpreted. We have mainly confined our attention to the determination of whether the heart is in a "vertical", "horizontal", "intermediate" or "indeterminate" position, and to the estimation of the degree of rotation round a longitudinal axis, i.e. clockwise or anti-clockwise as viewed from below.

According to Goldberger (1953) a QS, rS or rSr' pattern in V1, signifies a vertical heart, and a qR or QR pattern in VL a horizontal heart. Wilson (1946) classifies the patterns as follows:

Vertical heart.—VF resembles V5 and V6, and VL resembles V1 and V2.
Semi-vertical heart.—VF resembles V5 and V6, and in VL, QRS is small.
Horizontal heart.—VL resembles V5 and V6, and VF resembles V1 and V2.
Semi-horizontal heart.—VL resembles V5 and V6, and in VF, QRS is small.
Intermediate position.—VL and VF both resemble V5 and V6.

When R.V.H. is present the heart is usually vertical, leads V1 and V2 show an R or Rs pattern and therefore will not resemble the pattern in VL so that Wilson's criteria for the diagnosis of a vertical heart are unlikely to be fulfilled and under these circumstances are inappropriate. The explanation lies in the fact that Wilson's classification only considers rotation round the longitudinal and transverse axes.

In the combined operation series of 200 patients the heart was vertical or semi-vertical in 176, horizontal or semi-horizontal in 14, and intermediate or indeterminate in position in 10. In 90 per cent of the 177 patients with predominant stenosis the heart was vertical or semi-vertical, but of the 23 with predominant incompetence it was vertical or semi-vertical in 17, horizontal or semi-horizontal in 3 and indeterminate or intermediate in 3.

In the 14 patients in whom the heart was horizontal or semi-horizontal, and in the 10 in whom it was indeterminate or intermediate, some factor complicating mitral stenosis was usually present, e.g. mitral incompetence, aortic valvular disease, or obesity. In two the electrical position of the heart was an important factor in the diagnosis of biventricular hypertrophy as discussed below. Apart from its usefulness in this respect it is concluded that the electrical position of the heart is of little practical value in assessing the predominant defect at the mitral valve.

Clockwise Rotation. Clockwise rotation is usually diagnosed when the S normally present in V1–V3, persists as far round as V5 or V6 and aVR shows a QR pattern. The deeper the S or the greater the S/R ratio in leads over the left ventricle and the taller the R and the bigger the R/Q ratio in aVR, the greater the degree of clockwise rotation but in our experience these two signs by no means always accompany each other and we are uncertain as to the precise mechanism and relative significance of each.

Clockwise rotation is a matter of degree and is not uncommon in normal hearts. Extreme clockwise rotation usually signifies R.V.H. but there is no dividing line that separates with certainty physiological from pathological rotation. Nevertheless, there is general agreement that S>R in V5 and R>Q in aVR is abnormal. Similarly there are no absolute values for diagnosing an abnormal depth of S in V5 or an abnormal height of R in aVR.

From a detailed analysis of our material it is concluded that S>R in V5, or R>Q in aVR, and a depth of S in V5 of 5 mm. or more or a height of R in aVR of 3 mm. or more provide strong presumptive evidence for R.V.H.

TABLE I

INCIDENCE AND SIGNIFICANCE OF INDIRECT SIGNS OF R.V.H.

Indirect Signs			Direct Signs	
Sign	Lead	No. of Cases	No. of Cases	Percentage
R.A.D.=110° or more	I and III	20	20	100
R.A.D.=100°–109°	I and III	25	20	80
R+S=−3 mm. or less	I	33	33	100
R/Q>1	aVR	28	28	100
R=3 mm. or more	aVR	42	38	89
S/R>1	V5(6)	23	23	100
S=5 mm. or more	V5(6)	46	41	89

P WAVES

The upper range of normal for P wave height in the standard limb leads has been taken by various authors as 2·5–3 mm. and for breadth 0·1–0·12 sec. Broad, notched, or bifid P waves have long been recognized as a characteristic feature in patients with mitral valvular disease (P mitrale) and when pronounced in degree are almost diagnostic (Fig. 1). They were present in 106 of the 115 patients in sinus rhythm (92%). Presumably they result from atrial hypertrophy secondary to the mechanical results of mitral stenosis because frequently we have observed regression following successful valvotomy (Fig. 2). Reynolds (1953) suggests that the first peak of the bifid P wave derives from the right atrium and the second peak from

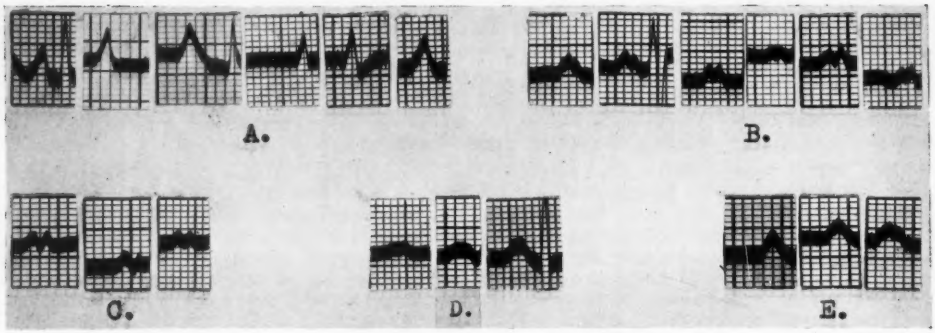


FIG. 1.—Abnormal P waves. (A)–(E). Different types.

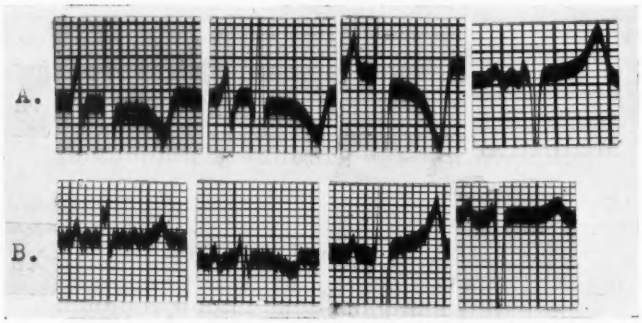


FIG. 2.—Regression of abnormal P wave patterns following valvotomy.
(A) Before operation. (B) After operation.

the left atrium. Broad and slightly notched P waves may be seen in hypertensive heart disease and Leatham (1950) reported slight notching in 17 per cent of his 100 normal cases although it was never pronounced. These observations make it impossible to be certain that such minor changes are pathological in a case of mitral valvular disease. Precise criteria cannot be laid down but in our consecutive series of 2000 unselected cardiograms we have observed marked changes such as those depicted in Fig. 1(B–E) in only two patients without mitral valvular disease: in neither was there a satisfactory explanation. In the operation series P waves taller than 3 mm. occurred in only 28 cases (14%). Tall, spiked P waves are commonly taken to indicate hypertrophy or dilatation of the right atrium and to be a particular feature of pulmonary and of congenital heart disease. In our series of patients with mitral disease P waves of this type were noted in 26 cases particularly in lead CR1 but there was no correlation between such P waves and the size of the right atrium, the degree of pulmonary hypertension or of R.V.H., and they were often associated with bifid P waves in other leads. They were not a constant feature even in those with tricuspid disease. P waves broader than 0·12 sec. occurred in only 10 cases. The occurrence and degree of severity of these abnormal P waves were compared with the size of the two atria, the degrees of mitral stenosis and incompetence, and the severity of pulmonary hypertension but there was no close or useful correlation. This is not perhaps surprising since atrial hypertrophy is presumably related to the duration as well as the degree of mitral valvular disease and may be present in the absence of radiological enlargement. In 11 instances abnormal P waves were recorded only in the præcordial leads. It is noteworthy that the only three patients with normal P waves in all leads had relatively mild pulmonary hypertension and mitral stenosis. However, there were 3 others with tight stenosis and considerable pulmonary hypertension who had normal P waves in the standard limb leads but those in the chest leads were abnormal.

The frequency with which abnormal P waves occurred in the various leads was analysed and also the leads in which the abnormalities were best shown. Their occurrence was so variable and their relationship to other features in the assessment so uncertain that these results are not presented in tabular form; and it is not profitable to discuss them in any detail. It should be mentioned that abnormal P waves of similar type occurred in 11 out of 12 patients in sinus rhythm who were operated on for predominant mitral incompetence. In most of the cases of mitral stenosis that we have regarded as too mild for surgical treatment, normal P waves have been present.

It is concluded that broad, notched P waves (especially in association with right axis deviation) are strongly suggestive of mitral disease and that entirely normal P waves are unlikely to be associated with severe stenosis but that a detailed analysis of P wave changes and the leads in which they occur is not of practical value in the assessment of patients for operation.

Q–T and P–R Intervals

Prolongation of the Q–T and P–R intervals in patients with rheumatic heart disease is commonly accepted as a sign of activity.

Q–T Interval. This was measured in leads I or II according to which showed the most clearly defined end of the T wave. Generally lead II was better than lead I for this purpose. Six successive cardiac cycles were analysed, the measurements being taken with the help of a ×6 lens. For each pair of cycles the Q–T and R–R intervals were measured and from this the QT*c* estimated (see below). The average of the five QT*c* intervals obtained was taken as the final measurement. In cases with sinus arrhythmia, in view of the variation in R–R intervals, 12 successive cardiac cycles were analysed. Cases with auricular fibrillation were excluded from this analysis in view of the variation in R–R intervals in most cases, the common difficulty in defining the end-point of T waves because of *f* waves interrupting the base line, and also because most of these cases were fully digitalized. Any case in whom salicylates, quinidine, or digitalis was being given was also excluded since these drugs are known to affect the QT*c*.

Correction of Q–T interval for heart rate was done by means of a nomogram based on Taran and Szilagyi's (1947) modification of Bazett's formula, $K=Q-T/c$ where c=cycle length and K=corrected QT, i.e. QT*c*. Ashman and Hull's (1941) criteria for the upper limit of the normal QT*c* were used in this series, i.e. 0·422 sec. for men and children and 0·432 sec. for women. Prolongation of QT*c* was present in 21 cases of the 115 in sinus rhythm, and the degree of this was as follows: 0·005 sec. or less in 4, 0·01 sec. or less in 11, 0·02 sec. or less in 17, and greater than 0·02 sec. in 4 cases.

Two cases had clinical evidence of rheumatic activity within a few months prior to operation, and the QT*c* was prolonged in one of them. Fourteen cases showed suggestive clinical evidence of rheumatic activity shortly after operation, and the QT*c* was prolonged in 3 of these pre-operatively and 7 post-operatively.

Twenty-seven cases in normal rhythm showed Aschoff bodies in the operative biopsy of the left auricle, and of these 5 had prolongation of QT*c*. A further 28 cases in normal rhythm showed cellular aggregates that were in various degrees of development and were accepted by the pathologist as indicating active rheumatism, although not amounting to the classical Aschoff body. Of these 28 cases, 7 had prolongation of QT*c* at the time of operation.

In 9 cases with prolongation of QT*c* at the time of operation there were no clinical signs of active rheumatism prior to or following operation and the biopsy was negative. In the operation series we found that positive biopsies of the left auricle for active rheumatism occurred twice as commonly in the 39 cases that developed post-operative auricular fibrillation as compared with those that did not. Only 5 of these cases had prolongation of QT*c* at the time of operation.

P–R Interval. Of the 16 cases with clinical evidence of active rheumatism a few months before or shortly after operation, prolongation of P–R interval occurred in only one. P–R interval was prolonged in only one of the 27 cases showing Aschoff bodies in the auricular biopsy, and in 2 of the 28 cases showing less clearly developed histological features of active rheumatism. Six cases had prolongation of P–R interval at the time of operation in whom there were no signs of active rheumatism prior to or following operation.

In only two cases were both the P–R interval and QT*c* prolonged at the time of operation: neither had clinical evidence of active rheumatism in the six months before operation or after operation, and one case had a negative and the other a positive left atrial biopsy without definite Aschoff bodies. *These findings demonstrate the inadequacy of the Q–T and P–R intervals in assessing rheumatic activity.*

Right Ventricular Hypertrophy

It is one of the main purposes of this paper to discuss the electrocardiographic signs of right ventricular hypertrophy (R.V.H.) because we have found that they usually signify the existence of considerable pulmonary hypertension, and that unless improvement can be obtained by operation, the outlook is poor. In the great majority of cases of rheumatic heart disease R.V.H. is secondary to tight mitral stenosis but occasionally, when pulmonary resistance is high, R.V.H. has been found in association with predominant mitral incompetence.

There have not been many papers that discuss criteria for the diagnosis of R.V.H. and none of the authors distinguish patterns produced by rheumatic heart disease from those secondary to other causes such as congenital heart disease and cor pulmonale. In rheumatic heart disease, not only is R.V.H. usually less severe than in these other conditions but in addition the mitral stenosis usually responsible for it is frequently complicated by co-existing mitral incompetence, aortic valvular disease, or rheumatic myocarditis, all of which may modify the cardiogram.

The electrocardiographic diagnosis of R.V.H. in patients in this series was primarily based on the criteria suggested by Wilson (1947), by Myers *et al.* (1948), by Sokolow and Lyon (1949 *a* and *b*), and by Carouso *et al.* (1951) and subsequently modified in the light of the analysis of our own clinical and post-mortem material. We have also taken into account analyses of normal unipolar cardiograms by Sokolow and Friedlander (1949), by Leatham (1950), and the authors quoted in *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels* (1953), and in our own department. Justification for the criteria accepted rests on presumptive evidence for R.V.H. based on clinical, radiological, and catheterization studies; and on regression of the various patterns following valvotomy and post-mortem correlation. The cardiogram was frequently normal in patients who on other grounds might be expected to have R.V.H. and in the post-mortem series there were 13 patients with R.V.H. anatomically but no evidence of this electrocardiographically. These matters are discussed below, but first it would seem appropriate to give the grounds on which a presumptive diagnosis of R.V.H. was made.

Presumptive Evidence for Right Ventricular Hypertrophy

(1) Palpable right ventricular thrust.
(2) Marked accentuation of pulmonary second sound.
(3) Marked enlargement of the pulmonary artery.
(4) Radiological signs of right ventricular enlargement.
(5) Considerable pulmonary hypertension.

Review of Published Criteria. Wilson *et al.* (1944) in their paper on the præcordial cardiogram in R.V.H. stated that in leads from the right side of the chest the R wave is large, Q frequently present, S usually absent, and T deflections commonly inverted. In leads from the left side of the præcordium the R deflections are abnormally small and the S deflections abnormally large. In other words, the præcordial electrocardiogram is the reverse of that obtained when the heart is normal. It is clear from our experience that this is the fully developed electrocardiographic pattern of R.V.H. Myers *et al.* (1948) analysed 40 cases of R.V.H. confirmed anatomically, 13 of which were due to mitral stenosis; they accepted the same criteria referred to above but do not give any absolute measurements. In 3 cases signs of R.V.H. were present in V3R only and in 2 in VE only. Complete or incomplete right bundle branch block were accepted as presumptive evidence for R.V.H. Sokolow and Lyon (1949) discuss 65 cases of R.V.H. diagnosed clinically. Absolute criteria for R.V.H. were laid down as follows: R wave >7 mm. or R/S ratio >1 in leads recorded over the right ventricle; S/R >1 in leads recorded over the left ventricle; R in V1+S in V5 $>10{\cdot}5$ mm.; R/S in V5 divided by R/S in V1 $<0{\cdot}4$. However, only 6 cases were due to mitral stenosis. The authors state that the diagnosis was made on clinical and radiological examination but make no reference to severity or to presumptive evidence for R.V.H. on other grounds. Carouso *et al.* (1951) analysed 58 post-mortem cases of which 24 were due to mitral stenosis. The R/S ratio was

>1 in V1 and <1 in V5 in 19 cases; >1 in V1 and normal in V5 in 11 cases; normal in V1 and <1 in V5 in 14 cases. In 14 cases the R/S ratio in the chest leads was normal but in 3 of these the T in V1, V2, V3 was negative or biphasic. Altogether such negative T waves were found in 18 cases and negative T waves in V1 and V2 in another 10.

Pagnoni and Goodwin (1952) accept R >S in V1 and a ventricular activation time in V1 > 0·03 sec. as direct signs of R.V.H., and consider S >R in V5 and a predominantly positive deflection in aVR as indirect signs indicative of extreme clockwise rotation or backward apical rotation, and virtually diagnostic of R.V.H. in the absence of cardiac infarction or right bundle branch block.

Indirect Signs. Our findings with regard to various indirect signs of R.V.H. have already been discussed and may be summarized by stating that right axis deviation>100°, an algebraical sum of R+S in lead I of −3 mm. or less, S/R>1 in V5, R/Q>1 in aVR, S in V5=5 mm. or more and R in aVR=3 mm. or more, all provide strong presumptive evidence for R.V.H. (Table I). Examples of complete regression of each sign are shown in Fig. 3.

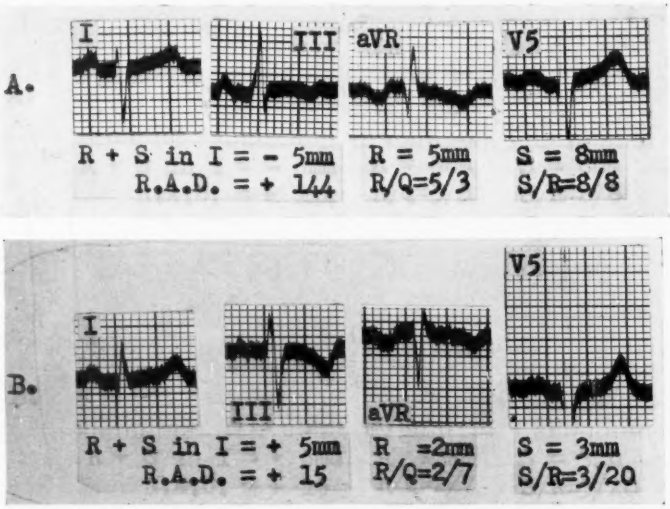


FIG. 3.—Regression of indirect signs of right ventricular hypertrophy following valvotomy. (A) Before operation. (B) After operation.

DIRECT SIGNS OF R.V.H.

R and S in Præcordial Leads. The points studied were the height of R, the depth of S and the R/S ratio. First, it is appropriate to refer to the leads in which R and S measurements are usually made when seeking information about ventricular hypertrophy. It is customary to take V1 and V5. We consider it better to select for these measurements those leads in which the changes are maximal, provided of course that one can be certain over which ventricle the electrode has been placed. Not only does the degree of rotation of the heart about its longitudinal axis vary from patient to patient, but the electrodes are of considerable size and to some extent must overlap with regard to the changes of potential that they pick up. Chests vary considerably in shape and size. Breasts may present difficulty from size, mobility, and tissue resistance, and in practice technicians, who are usually responsible for recording the cardiograms, cannot be absolutely precise as to the positions where the electrodes are placed. Moreover, the thickness of the wall of the right ventricle is not uniform all the way round. In this series cardiographic changes of R.V.H. were found in V1 in 85 of the 115 cases (74%).

In our experience, changes attributable to R.V.H. may be more marked in V2 (and occasionally in V3) than in V1. One must, of course, be certain that V2 is being recorded over the right ventricle. In this series changes in V2 provided the sole evidence of R.V.H. in 4 cases and better evidence than V1 in 20 cases. The value of right-sided V leads (V3R, V4R, VE) is discussed below.

Similarly, changes directly attributable to L.V.H. and the depth of S indirectly suggesting R.V.H. may be more marked in V4 or V6 (recorded over the left ventricle) than in V5.

Most authors express their findings in tables which give maximum, minimum, and mean values for height of R and depth of S.

TABLE II

SIZE OF R AND S WAVES IN 560 HEALTHY ADULTS (8 AUTHORS*)

	R			S		
	Min.	Max.	Mean	Min.	Max.	Mean
V1	0	15·5	3·1	0·8	26·2	9·4
V2	0	23·0	6·0	0	39·2	14·1
V5	0·4	33·6	12·0	0	16·1	2·0
V6	2·0	22·6	9·7	0	14·3	1·0

* Taken from *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels* (1953), p. 178.

The number of cases in the upper, lower and intermediate ranges are rarely included. It is certain that maximum values in normals are far greater than the mean values in ventricular hypertrophy and that the electrocardiographic diagnosis of ventricular hypertrophy would rarely indeed be made if only values above the upper range of normal were accepted. It must, therefore, be concluded that absolute criteria of practical value for the electrocardiographic diagnosis of ventricular hypertrophy are impossible to deduce from most published tables. Tables that give the scatter in the various ranges are more useful but even then conclusions as to presumptive evidence for ventricular hypertrophy on electrocardiographic grounds can only be based on high probability. Nevertheless, in practice, presumptive evidence for ventricular hypertrophy on one criterion may be provided and serve as a useful stimulus to look with particular care for other cardiographic evidence and may materially influence the overall assessment of the patient.

Right Ventricular Leads

In right ventricular hypertrophy (R.V.H.) the R waves in leads recorded over the right ventricle are characteristically tall and the S is small. All authors refer to the R/S ratio in V1 but only Sokolow and Lyon (1949) consider the absolute height of R and they do not refer to the diagnostic significance of a tall R in cases in which the R/S ratio<1. Most authors only refer to lead V1.

R/S Ratio. As mentioned above R/S >1 in RV leads is generally accepted as a sign of R.V.H. In normal adults Leatham (1950) found R/S in V1 was always<1 and the maximum ratio recorded by Sokolow and Friedlander (1949) was 1. In our consecutive series of 2000 cardiograms R/S>1 was not found in any patient without some pathological condition likely to give rise to R.V.H. In the post-mortem series all 14 cases with R/S>1 had anatomical R.V.H. In the operation series R/S in V1 was>1 in 61 cases and in V2 (recorded over the right ventricle) in an additional 3, all of whom had strong presumptive evidence for R.V.H. on other grounds; we have never found R/S>1 in a patient with mitral stenosis in the absence of such presumptive evidence. In 16 (additional) cases this criterion was only present in V3R, V4R, or VE. It may be worth emphasizing that even if the absolute height of R is small, R/S>1 signifies R.V.H. (Fig. 4). In the operation series there were 22 such cases in which R was <5 mm. and this included 12 with R$=4$, 6 with R$=3$, and 4 with R$=2$. Our experience therefore confirms the value of the R/S ratio. It is noteworthy that of

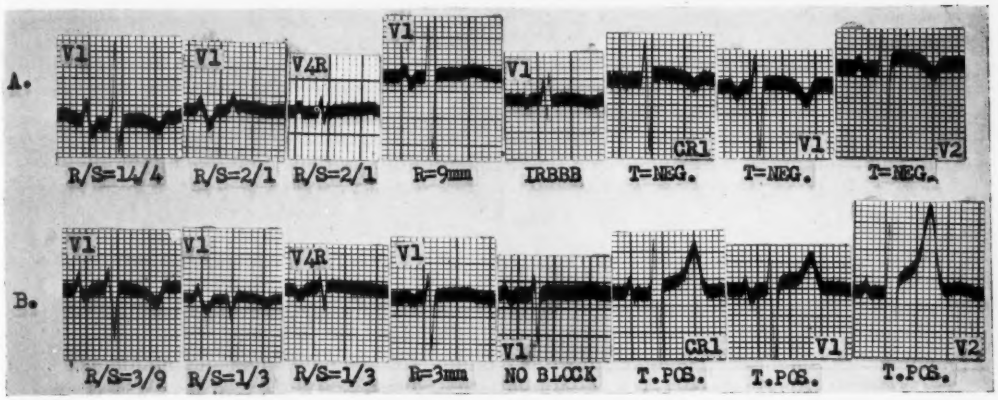


FIG. 4.—Regression of patterns of right ventricular hypertrophy following valvotomy. (A) Before operation. (B) After operation.

115 cases in which an electrocardiographic diagnosis of R.V.H. was made on the criteria recommended in this paper, the R/S ratio was<1 in 33 (29%).

Absolute Height of R. Leatham (1950) found the upper limit of normal for R waves in V1 was 8 mm. and Sokolow and Friedlander (1949) 7 mm. but Graybiel *et al.* (1952) state that R may be 10 mm. high in health. Table II gives a maximum value for R in V1 of 15·5 mm. This far exceeds the mean and maximal values quoted by most authors. We have studied the source from which this table was compiled and it appears that this maximal figure refers to an exceptional single case quoted by one author.

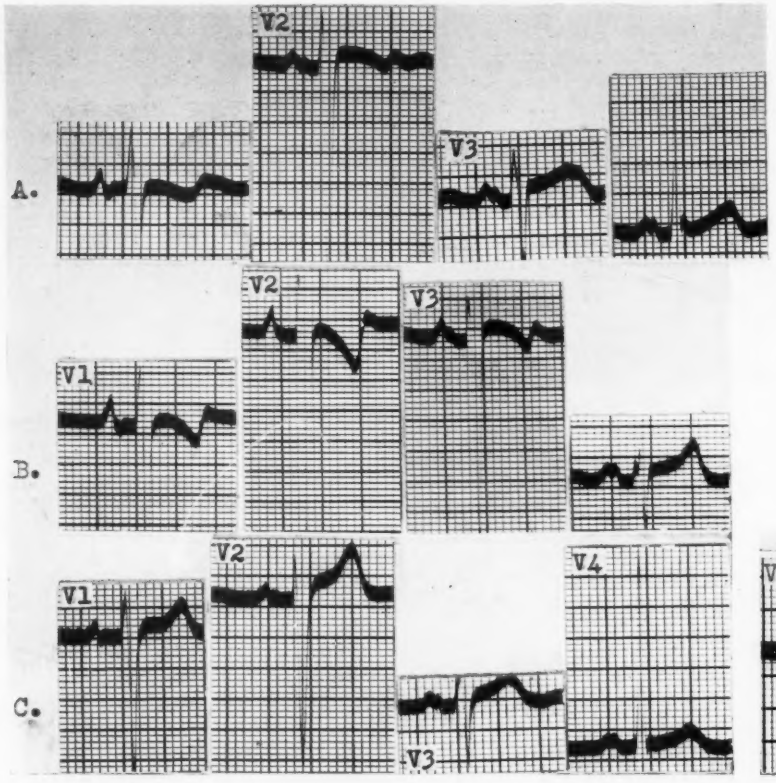
In the 64 cases in the operation series in whom R/S>1 in V1(2), R was more than 10 mm. in 13 and 7–10 mm. in 15. It is noteworthy that in the 115 cases in which an electrocardiographic diagnosis of R.V.H. was made the absolute height of R was 4 mm. or less in 58 (49%).

Sometimes the R and S waves are both of exceptionally high voltage. Since in R.V.H. the S wave in V1(2) is characteristically small or absent, when a deep S (as in Fig. 5) accompanies a tall R, we felt reluctant at first in accepting its significance as a sign of R.V.H. but we have observed regression after operation, and in the post-mortem series all cases (11) with R>7, irrespective of the R/S ratio, had marked anatomical R.V.H. (Fig. 6).

In the operation series there were 10 patients in whom R>7 mm. in V1 was associated with a deep S so that the R/S ratio<1. It is noteworthy that not only was there a deep S wave in V1 but that the clockwise rotation so commonly present in patients with R.V.H., as judged by an S wave over the left ventricle, was absent in all but one of these cases. This suggests that the pattern is influenced by the electrical position of the heart. However, it does not influence our conclusion from all the evidence quoted above that an absolute height of R>10 mm. in leads recorded over the right ventricle almost certainly indicates the presence of R.V.H. and one>7 mm. is strongly suggestive.

Left Ventricular Leads. In R.V.H. the S waves in leads recorded over the left ventricle tend to be deeper and to present further to the left than in normal hearts, i.e. as far round as V5, V6, or V7. How far to the left the S is recorded is a measure of clockwise rotation and hence indirectly often a sign of R.V.H. as already discussed.

In our series the mean depth of S in V5 was 4·1 mm. (0–33) and in V6 1·8 mm. (0–20) for those with R.V.H., and for those without R.V.H. 1·1 mm. (0–10) in V5, and 0·1 mm. (0–3) in V6 respectively.



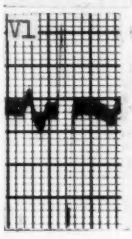


FIG. 5 FIG. 6

FIG. 5.—Progression of right ventricular hypertrophy before operation and regression afterwards. (A) 29/3/50, before operation. (B) 14/3/51, before operation. (C) 31/7/51, after operation.
FIG. 6.—Right ventricular hypertrophy. Tall R and deep S in V1. R/S=12/16 mm. Post-mortem contro confirmed R.V.H.

Sokolow and Lyon (1949) state that R.V.H. may be suspected when S>R in V5, and also consider that certain combined measurements are of value in this respect, i.e. R in V1+S in V5> 10·5 mm. and the ratio of R/S in V5 divided by R/S in V1<0·4. Pagnoni and Goodwin (1952) also consider that S>R in V5 is a valuable indirect sign of R.V.H. These criteria have been considered in all our cases but in no instances do they give positive information in the absence of other electrocardiographic signs of R.V.H.

Right-Sided V Leads. When the conventional præcordial leads do not provide evidence of R.V.H. or the signs are equivocal, it is worth while recording leads from other positions on the chest wall (Fig. 7). We have studied the value of V3R, V4R, and VE. V3R and V4R are recorded to the right of the sternum in the intercostal positions corresponding to V3 and V4 on the left. VE is recorded over the ensiform cartilage (Fig. 8). Myers *et al.* (1948) noted that V3R alone gave positive cardiographic evidence of R.V.H. in 2 out of 40 autopsy cases, and Barker and Valencia (1949) showed that V3R, V4R, and VE were sometimes of decisive importance in the detection of incomplete right bundle branch block.

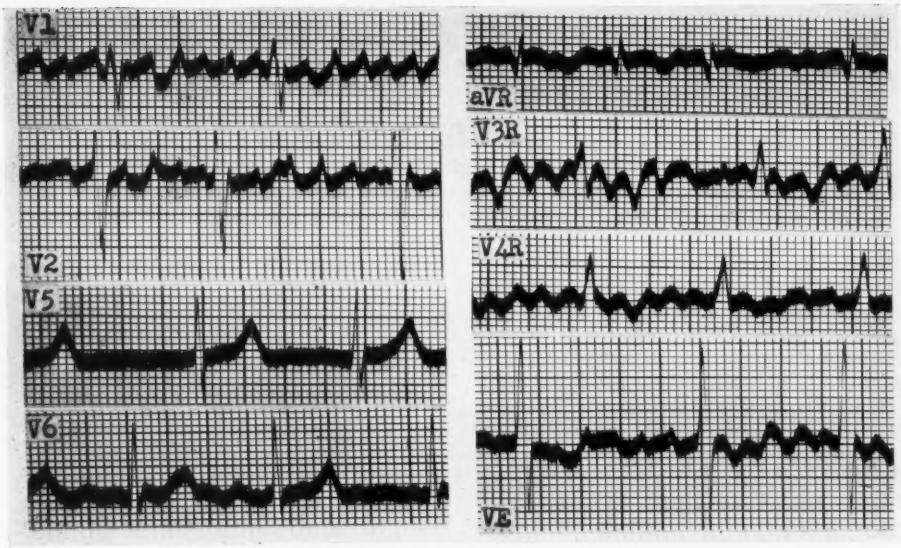


FIG. 7.—Right ventricular hypertrophy. To illustrate the value of right-sided V leads. The only possible indication of R.V.H. in the conventional leads is a slight degree of incomplete right bundle branch block in V2. V4R is diagnostic of R.V.H.

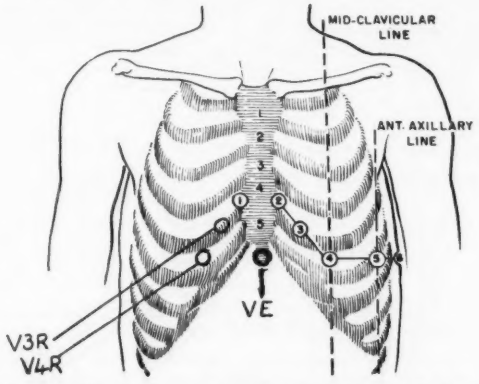


FIG. 8.—The electrocardiographic diagnosis of R.V.H. was made in 115 of the 177 cases of mitral stenosis (65%). Right-sided V leads were recorded in 95 of these 115 (83%) and were positive in 76 of the 95 (80%). V4R was positive in 73 of the 76 in which it was recorded (96%). Right-sided V leads were positive and the sole sign of R.V.H. in 16 of the 95 (17%).

V3R, V4R, and VE were recorded pre-operatively in 141 patients in our series and in 95 of the 115 cases in which a cardiographic diagnosis of R.V.H. was made. In 76 of the 95 the R/S ratio>1 in one or more of these leads. All had strong presumptive evidence of R.V.H. on grounds other than electrocardiographic. R/S>1 has never been seen in the absence of such evidence. In the post-mortem series, anatomical evidence of R.V.H. was present in each of the 11 cases in which this

ratio had exceeded unity. Accordingly an R/S >1 in V3R, V4R, or VE has been accepted as a positive criterion for R.V.H. In 16 of the 115 cases, positive findings in these leads were the sole electrocardiographic sign (Fig. 9). The right-sided V leads more frequently gave evidence of R.V.H. than any other leads but in 11 cases where the usual præcordial leads provided evidence of R.V.H. this was lacking in the right-sided leads.

It is concluded that when R.V.H. is suspected on clinical grounds but not revealed in the customary præcordial leads, significant changes may be found in V3R, V4R, or VE in 15–20 per cent of the cases; but that from the practical point of view, since V4R was positive in 96 per cent of the cases in which right-sided V leads gave evidence of R.V.H., it will usually be sufficient to record V4R.

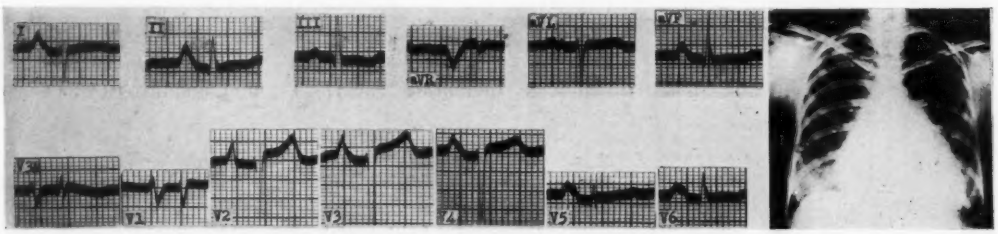


FIG. 9.—Considerable cardiac enlargement (cardio-thoracic ratio 62%). Sole sign of right ventricular hypertrophy in V3R. Tight mitral stenosis.

It is of interest that an electrode placed in the fifth right intercostal space in the mid-clavicular line should serve so well in providing evidence for R.V.H. This emphasizes the present lack of knowledge of the precise mechanism of the genesis of electrocardiographic signs of R.V.H. Goldberger (1945), Kossman *et al.* (1948), and McGregor (1950) discuss this problem and the last author suggests that the electrocardiographic pattern of R.V.H. may be due to pronounced rotation of the heart with almost complete reversal of the electrical fields of the two ventricles in the thorax. In many of our cases, however, there was no other evidence to suggest that such a large degree of rotation was present and it is uncommon for the surgeon undertaking valvotomy to detect such a conspicuous change of position, e.g. with reference to the position of the descending branch of the left coronary artery.

Q Waves. Myers *et al.* (1948) state that a Q in V1 is common in R.V.H. but Donzelot *et al.* (1951) found it in only 70 per cent and Woods (1952) in 15 per cent of cases of Fallot's tetralogy. In our series a Q in V1 occurred in 19 cases all of which had other cardiographic signs of R.V.H., i.e. it occurred in 19 out of 177 cases (11%) of mitral stenosis and in 19 out of 95 (20%) of those in whom an electrocardiographic diagnosis of R.V.H. was made. In an additional 10 cases a Q wave was present only in V3R or V4R. Four of the post-mortem cases showed a Q in V1 and the relation between this and the thickness of the right ventricular wall was as below.

R/S in V1	8/0	3/1	8/0	11/0
R.V. thickness (mm.)	9	11	12	9

Each case had strong presumptive evidence for R.V.H. but in the series as a whole there was no close correlation between this and the presence or absence of Q waves.

RIGHT BUNDLE BRANCH BLOCK

Right bundle branch block (R.B.B.Bl.) is usually diagnosed when leads over the right ventricle show primary (R) and secondary (R′) waves separated by a downward deflection, when there is no Q wave, and when the ventricular activation time (V.A.T.) is prolonged. Most authors differentiate complete from

incomplete block according to whether QRS is 0·12 of a second or more or less than this in duration. However, incomplete block is a matter of degree and merits further discussion. Polyphasic complexes are common but there are no agreed criteria as to what constitutes incomplete block nor as to the significance that can be attached to this finding. A wide variety of polyphasic complexes may be seen and not always is the total duration of QRS or the V.A.T. prolonged. Tall initial or secondary upward deflections are usually designated as R and R′ respectively and similar but small complexes as r and r′. Carouso *et al.* (1951) state that complexes that include a tall R suggest R.V.H. but that patterns of types rSr′, rsr′, rsr′s′ and M cannot be accepted as evidence of this. In one of the tables in their paper it is clear that the designation of R was given to a wave of 2 mm. amplitude and presumably all R waves >2 mm. are to be designated likewise. We have been unable to find any reference to absolute measurement for deciding whether an R or r wave is " tall " or " short ". According to Barker and Valencia (1949) R.V.H. associated with incomplete R.B.B.Bl. (I.R.B.B.Bl.) can be diagnosed when the secondary R wave (R′) is >10 mm. in height. Carouso *et al.* show that this criterion is too severe because R.V.H. was found anatomically in 21 of 24 cases with I.R.B.B.Bl. that would not have been classified on these electrocardiographic grounds as

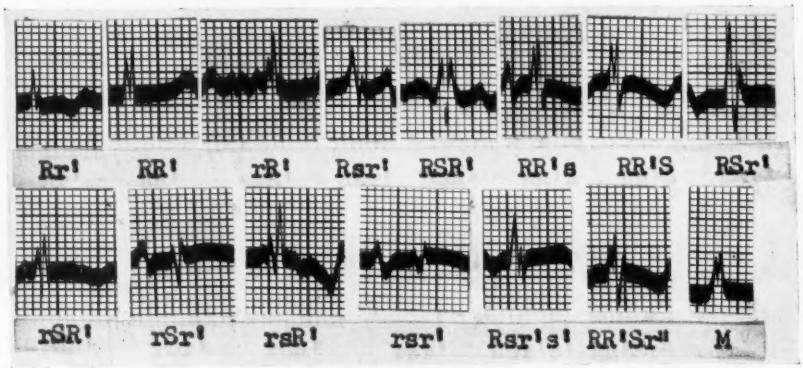


FIG. 10.—Patterns of incomplete right bundle branch block (Lead V1).

having R.V.H. Myers *et al.* (1948) state that in the chest leads of patients with I.R.B.B.Bl., QRS <0·12 sec. and V.A.T.=0·05 to 0·075 sec. Wilson (1947) states that the QRS is 0·09 to 0·11 and Carouso *et al.* state that QRS <0·11 and V.A.T. is prolonged.

In some subjects the QRS is normally less than the more usual 0·08 sec. in chest leads. If bundle branch conduction is impaired in such an individual it is clear that a normal of 0·08 sec. would in fact represent delayed conduction although by customary definition this would not be accepted as a case of bundle branch block.

Occasionally I.R.B.B.Bl. has been reported in perfectly normal persons. Pathologically it occurs most commonly in rheumatic, ischæmic, and congenital heart disease and may be seen transiently in acute cardiac dilatation. We have not recorded a full series of cardiograms in a sufficiently large number of normal subjects but believe that polyphasic complexes must at least be very uncommon in health. We have analysed the cardiograms in 2000 consecutive cases and polyphasic complexes over the right ventricle with QRS <0·12 sec. were found in 60 instances as follows, but never in the absence of one of these conditions: ischæmic heart disease (16 cases), cor pulmonale (13), atrial septal defect (6), ventricular septal defect (5), constrictive pericarditis (8), and mitral stenosis (12 cases).

In this series of 200 cases with mitral stenosis subjected to valvotomy complete R.B.B.Bl. were recorded in one case and polyphasic complexes QRS <0·12 sec. (I.R.B.B.Bl.) in 45 cases. In 10 V.A.T. was <0·05 sec. and in 35 it was 0·05 sec. or more in duration. A considerable variety of patterns occurred and included the following: Rr′, RR′, rR′, Rsr′, RSr′, RSR′, RsR′, RR′s, rSR′, rSr′, rsR′, rsr′, RR′sr′′, Rsr′s′ and M (Fig. 10). Difficulties may sometimes arise in cases with auricular fibrillation in which *f* waves are superimposed on the QRS complex. In cases of doubt close inspection of all the complexes in V1 and if necessary the recording of lead CR1 will serve to distinguish the two patterns (Fig. 11).

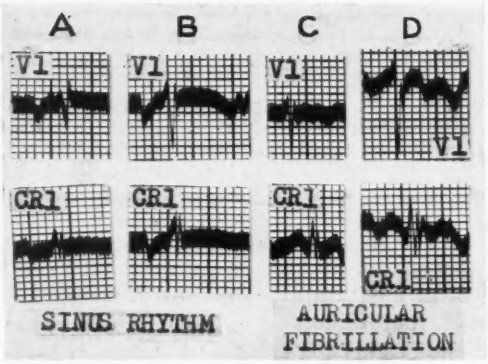


FIG. 11.—CR1 confirming doubtful pattern of incomplete right bundle branch block in V1. (A)–(D) are from four different cases.

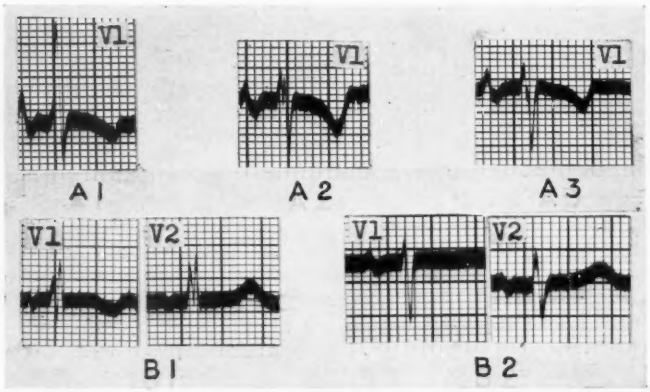


FIG. 12.—(A) Development and regression of incomplete right bundle branch block; (A1) before operation, (A2) 6 months after operation, and (A3) 12 months after. (B) Regression of incomplete right bundle branch block; (B1) before operation, and (B2) 18 months after.

In the post-mortem series, there were 11 examples of I.R.B.B.Bl. and anatomically all had definite R.V.H. Moreover, in the operation series of 200 patients and in a parallel series of 200 patients not subjected to operation we have never seen I.R.B.B.Bl. in the absence of strong presumptive evidence for R.V.H. on clinical and radiological grounds. After operation the pattern may regress (Fig. 12).

Further support for this criterion is given by the examples shown in Fig. 13, in which it will be seen that the pattern of I.R.B.B.Bl. in V1 is accompanied by a strongly positive R/S ratio in CR1 or in V4R or VE.

For all these reasons it is concluded that although in patients with mitral stenosis the pattern of I.R.B.B.Bl. cannot be accepted as definite direct evidence, because it is possible that it may be due to a defect of conduction from rheumatic myocarditis or ischæmia, from the practical point of view it is unlikely to be found except in the presence of R.V.H.

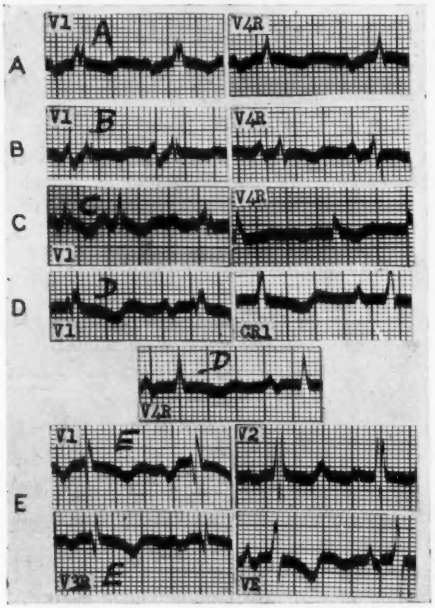


FIG. 13.—Electrocardiographic diagnosis of right ventricular hypertrophy. Illustrating the value of right-sided V leads (V3R, V4R, VE). The pattern of incomplete right bundle branch block in V1 is associated with a strongly positive R/S ratio in the right sided V leads.

NEGATIVE T WAVES

Negative T waves in leads recorded over the right ventricle commonly accompany other electrocardiographic signs of R.V.H. Myers *et al.* (1948) state that a negative T in V1 cannot by itself be attributed to R.V.H. unless characteristic changes in the QRS complex are also present. Our experience confirms that of Leatham (1950) and of Myers *et al.* (1948) that occasionally the T wave in V1 may be negative in health although under these circumstances it is never, after childhood, more than 2·5 mm. in depth.

Out of this series of 200 patients subjected to operation in whom there was no other cardiographic evidence of R.V.H. but presumptive evidence for such hypertrophy on other grounds, a negative T in V1 was accompanied by a negative T in V2 in 5 patients and by a negative T in V2 and V3 in 2 patients, by a negative T wave in CR1 in 7 cases and in both CR1 and V2 in 5 patients. The 7 patients in whom T was negative in CR1 and V1 have not been included in the number of positive cases because we consider the evidence suggestive rather than conclusive.

It is appreciated that similar T wave inversions may occur in so-called right ventricular strain, e.g. acute cor pulmonale. The term right ventricular " strain " commonly applied to such negative T waves is not satisfactory because " strain " has no precise connotation. It might presumably arise from dilatation, anoxia, ischæmia, or from biochemical changes. In the patients under consideration no acute episodes had occurred and in all except one the changes were persistent and sometimes progressive. In one patient the changes receded during a period of rest in hospital. Following valvotomy these signs sometimes regress (Fig. 5).

It is concluded that in patients with mitral stenosis in the absence of any other obvious cause such as acute cor pulmonale, pericarditis, or myocardial infarction, a negative T wave in VI if accompanied by a negative T in V2 can be taken as presumptive, and in CR1 as suggestive, evidence of R.V.H.

Myocarditis Pattern

It is difficult to prove that an electrocardiographic pattern can be attributed to fibrotic changes resulting from rheumatic myocarditis. We have suspected an abnormal T wave pattern in 4 cases (Fig. 14) in the absence of any other obvious cause, the persistence of the pattern after a successful

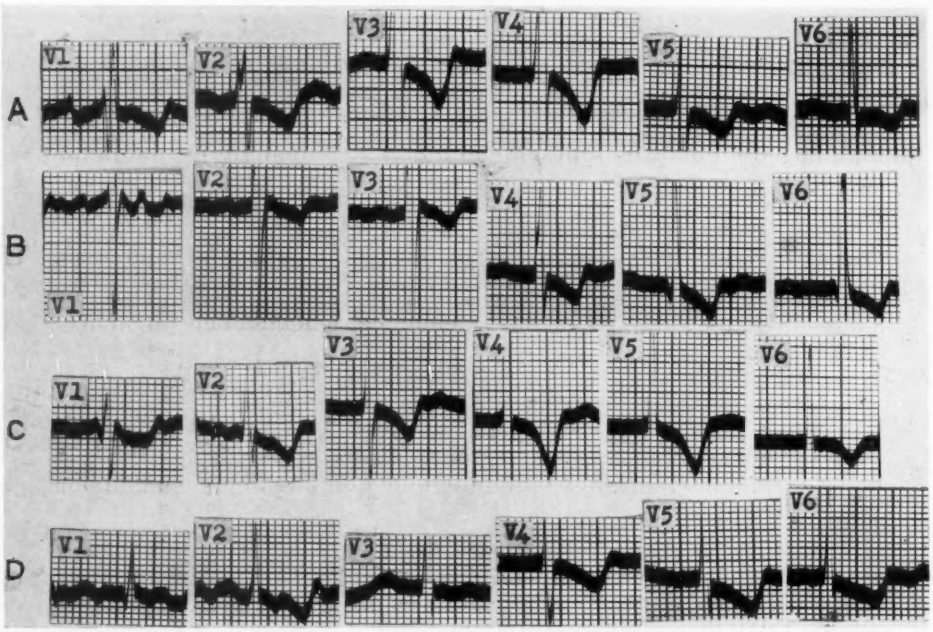


Fig. 14.—Negative T waves. ? Fibrosis pattern.

valvotomy, and in one case by correlation with post-mortem findings. The pattern is similar in the 4 cases and not characteristic of ventricular hypertrophy or that usually resulting from digitalis. Case 6 was the only one on digitalis. No cause for L.V.H. was present in any of them.

This pattern is uncommon in spite of the presumed frequency of rheumatic myocarditis, and in 7 cases we have studied in which microscopical changes attributable to old rheumatic myocarditis were reported by the pathologist, no suggestive cardiographic changes were recorded.

Ventricular Activation Time

The time interval measured from the commencement of the Q wave to the peak of R (or in cases where there is no Q wave, from the beginning of R to the peak of R) is termed the " ventricular activation time " (V.A.T.) and is commonly considered to be an expression of the thickness of the ventricular wall underlying the electrode.

In lead V1 (or V2) over the right ventricle, the V.A.T. is normally $<0{\cdot}03$ sec. (Myers *et al.*, 1947; Sokolow and Friedlander, 1949; Carouso *et al.*, 1951; Kossman, 1953) and an increase in this time above the normal

is taken to indicate R.V.H. (Myers *et al.*, 1948; Sokolow and Lyon, 1949). The V.A.T. has been measured in all cases in this series but in the 115 cases with electrocardiographic evidence of R.V.H., a V.A.T. >0·03 sec. was found in only 62. In 45 of them, this was associated with polyphasic QRS complexes. In no case was the V.A.T. abnormal in the absence of other electrocardiographic signs of R.V.H. Presumably this is due to the fact that in spite of considerable R.V.H. the width of the free wall of the left ventricle is still greater than that of the right ventricle and hence tends to neutralize the potential electrocardiographic signs of R.V.H. The V.A.T. was often normal in cases with clear-cut cardiographic signs of R.V.H. on other grounds.

Myers *et al.* (1948) suggest that V.A.T. in V1 which is greater than that in V5 or V6 indicates R.V.H. In our series when V.A.T. in V1 was 0·05 sec. or greater, it always exceeded that in V5, but in 3 cases where V.A.T. in V1 was 0·04 sec., it did not exceed that in V5 although R.V.H. was definitely present on other cardiographic grounds. It is, therefore, concluded that as a sign of R.V.H. an increased V.A.T. in V1 need not, in addition, be greater than that in V5. Two of these three showed V.A.T. in V1 the same as that in V5 (0·04 sec.) and in the third case, which had complete R.B.B.Bl., it was 0·05 sec. in V5. Woods (1952) in cases of tetralogy of Fallot found that in 96 per cent V.A.T. in V6 was either less than (94%) or equal to (2%) V.A.T. in V1. This emphasizes the difference between the incidence of prolongation of V.A.T. in V1 in congenital pulmonary stenosis and that in mitral stenosis. In most of the papers in which reference to the V.A.T. is made, R.V.H. due to congenital heart disease, cor pulmonale, and mitral valvular disease have been grouped together.

It is concluded that in patients with mitral stenosis, the degree of R.V.H. is relatively less than that which occurs in, e.g. congenital heart disease or cor pulmonale, and that this measurement is of little practical value.

Depression of the S–T Segment

Depression of the S–T segment below the iso-electric line in leads recorded over the right ventricle may be found in association with other electrocardiographic signs of R.V.H. and occurred in 13 patients of this series. No significance to this finding *per se* can be paid in those taking digitalis. Transient depression from ischæmia is discussed below. In patients with R.V.H. from congenital heart disease, particularly in pulmonary stenosis with an intact ventricular septum, tall R and negative T waves are commonly associated with S–T depression and it might be thought that S–T depression was a measure of severity. In this series of patients with mitral stenosis, S–T depression >0·5 mm. was recorded in only 13 cases, in 9 of whom the R wave was >7 mm. and in 4 of these was R >10 mm. None was taking digitalis. All these cases had severe mitral stenosis with considerable pulmonary hypertension, all had cardiographic signs of R.V.H., and the pattern was well developed in 11. One case came to necropsy; the thickness of the right ventricle was 9 mm. and the left ventricle was 12 mm., and the heart weight was 560 g.

It is concluded that S–T depression from right ventricular hypertrophy occurs only when the latter is gross, but since it is absent in many cases known to have considerable hypertrophy, it is an unimportant sign in patients with mitral stenosis.

Grading of R.V.H.

After analysing the electrocardiographic changes in each case we attempted to grade the degree of severity of R.V.H. but found the task impossible. In the first place one cannot be sure of the relative importance of the various criteria for R.V.H.

It would seem reasonable to assume that the taller the R and the greater the R/S ratio over the right ventricle, the greater the degree of R.V.H. but certainly the converse does not hold. In the operation series there was a wide discrepancy between cardiographic signs of R.V.H. and presumptive evidence for it on other grounds. In the post-mortem series there were 18 patients in which the thickness of the right ventricular wall was 8–12 mm. and in this group the height of R varied indiscriminately between 1–15 mm. and the R/S ratio from 0·1 to 11·0.

The detailed findings in all our post-mortem cases with adequate cardiographic and autopsy measurements are shown in Table III. The lack of correlation between electrocardiographic signs of R.V.H. and the presence of anatomical R.V.H. is striking, and in particular the correlation between the better developed cardiographic signs of R.V.H. and the more pronounced degrees of anatomical R.V.H. is seen to be poor.

Similar findings in relation to cases of the tetralogy of Fallot with post-mortem studies have been noted

by Donzelot *et al.* (1951) (10 cases), and Woods (1952) (7 cases). Pagnoni and Goodwin (1952) also comment on this disparity in their series of cases with biventricular hypertrophy.

It is probable that in the pattern commonly taken to indicate incomplete right bundle branch block the absolute height of R and the R/S ratio have the same significance as when block is not present.

TABLE III

CORRELATION OF RIGHT VENTRICULAR HYPERTROPHY AND R/S IN V1 AFTER NECROPSIES (36)

Case No.	Heart weight (g.)	Thickness (mm.) of		R/S in V1
		R.V.	L.V.	
3	650	+	+	0/6
35	560	5	13	1/13
38	600	12	14	6/1
43	340	8·5	15	3/0
52	320	6	10	12/16
57	500	13	15	8/2
79	560	9	12	8/0
87	400	+	+	7/15
91	650	8	12	1/6
96	490	11	12	3/1
99	380	5	15	1/8
107	650	15	30	8/31
114	610	8	20	0/4
116	500	12	21	2/5
145	500	9·5	11	0/11
147	680	11	10	3/1
162	580	12	13	15/1
168	600	7	15	1/14
170	460	7	16	6/12
185	440	10	15	7/1
186	560	5·5	13	0/9
187	660	5	13	2/5
188	480	12	16	8/1
196	770	9	13	11/0
A	520	++	N	10/16
B	520	+	+	1/19
C	600	++	+	1/2
E	500	6	11	1/5
F	340	+	N	2/6
G	400	+	N	6/9
I	650	+	++	1/10
J	740	8	16	1/6
K	—	++	N	12/0
L	500	12	15	6/0
M	485	8·5	13	1/8
N	—	10	14	1/4

The significance of T wave changes is very difficult to determine. Negative T waves have sometimes been associated with a severe right ventricular hypertrophy pattern as judged by R and R/S, and in other cases with a similar severe pattern they have remained upright. Sometimes negative T waves have been the sole sign of R.V.H. and have regressed after valvotomy, and sometimes an atypical pattern has been considered to be related to rheumatic myocardial changes.

The probable basis for the difficulties encountered are discussed in this paper and include the varying degrees of left ventricular hypertrophy from associated mitral incompetence or aortic valvular disease and changes secondary to rheumatic myocarditis. In the operation series the evidence for R.V.H. other than electrocardiographic is necessarily presumptive although we are satisfied that the grounds given for presumption are secure. In the post-mortem series there are also difficulties related to ventricular wall thickness and to dilatation and to heart weight and these factors too are discussed.

TABLE IV

ELECTROCARDIOGRAPHIC SIGNS OF R.V.H. (115 CASES)

Direct signs	Total No. of cases	Percentage in which positive	Sole criterion
Height of R			
R>7 mm. in V1	38	33	10
R/S>1	28		8
R/S<1	10		2
R>7 mm. in V2* but not in V1	10	12	1
R/S ratio			
R>S in V1	61	53	
R>S in V3R, V4R, or VE	76**	80**	16
R>S in V2* but not in V1	3		0
V.A.T.			
V.A.T.>0·03 sec. in V1	62	54	0
V.A.T. in V1>V5	42	36	0
Probable signs			
Right B.B.Bl.	45	39	7
Complete	1		0
Incomplete	44		7
B.B.Bl. in V2 but not in V1	4		0
Negative T waves	49	43	7
V1 and V2	19		
V1, V2, and V3	30		
Indirect signs			
R.A.D.>100°	40	35	0
R+S in I=or <−3 mm.	33	28	0
R>Q aVR	28	24	0
R=or> 3 mm. aVR	42	36	0
S>R V5	23	20	0
S=or>5 mm. V5	46	40	0

* Recorded over the right ventricle.

** Right-sided V leads were recorded in only 95 of the 115 cases with R.V.H. B.B.Bl.=Bundle branch block. R.A.D.=Right axis deviation. V.A.T.=Ventricular activation time.

FACTORS THAT INFLUENCE THE DEVELOPMENT OF R.V.H.

The cardiac output and the resistance against which the right ventricle must work are the principal factors that influence the development of hypertrophy of the right ventricle. The cardiac output is related to physical activity and to emotion, both of which vary widely in different patients. Young persons in particular are naturally active and in our experience many of the most extreme degrees of R.V.H. come from this group. Others, knowing that heart disease is present and fearing the consequences, or from the discomfort engendered by exertion, lead exceptionally quiet lives and thus limit their cardiac output.

The degree of obstruction at the mitral valve is the most obvious reason for an increase in pulmonary arterial pressure, but not the only one. Pulmonary arteriolar narrowing is a second important factor and seems to vary independently. The size and distensibility of the left atrium also influence the pressure changes that develop in the pulmonary vessels. Post-rheumatic myocardial changes must limit contractility of the right ventricle in many cases, and chemical and

endocrine changes, about which little is as yet known, are probably more important than at present realized.

The various factors that contribute to R.V.H. are, therefore, neither simple, few, nor mutually unrelated, and account for the variability of R.V.H. in patients with an apparently similar degree of mitral stenosis. It is an old observation that many patients with mitral stenosis, even of severe degree, do not show electrocardiographic signs of R.V.H. In this series of 177 consecutive patients who were considered to be sufficiently disabled for submission to valvotomy, electrocardiographic signs of R.V.H. as detailed above were observed in 115. For reasons discussed above, it was considered probable that some degree of R.V.H. was in fact present in most of them. Admittedly the evidence is presumptive, but the presumption is strong and the inference is supported by post-mortem examination in clinically similar cases in whom a full series of cardiograms had been recorded. From the study of our material, it is concluded that electrocardiographic signs do not occur until hypertrophy is marked and that in mitral stenosis hypertrophy is frequently less severe than in congenital heart disease.

The essence of the difference between the two conditions in respect of the cardiographic pattern of R.V.H. is that in pulmonary stenosis an initially healthy muscle has had to overcome a greater resistance for a longer period. In some cases, as discussed in the section on biventricular hypertrophy, the development of the pattern of R.V.H. is prevented by the presence of L.V.H. from mitral incompetence, aortic valvular disease, or essential hypertension.

Difficulties in Post-mortem Studies

The difficulties of accurate correlation between electrocardiographic and anatomical findings are not always fully appreciated, and little emphasis has been made regarding this in writing. Tables are available giving the average weight of the heart compared with body weight in healthy subjects of each sex. Many patients with severe mitral stenosis are thin from loss of weight, but it is problematical to what extent heart weight is affected by general loss of body weight.

We have accepted as definite evidence of ventricular hypertrophy a thickness of the muscle on the right of 5 mm. and on the left of 13 mm. for an average body weight of 140 lb. (65 Kg.).

It is perfectly clear that when the heart weight considerably exceeds the normal, as it did in most of our post-mortem series, ventricular hypertrophy exists even though the thickness of the ventricular walls is within the accepted normal range. At an ordinary necropsy, even when particular attention is being paid by the pathologist and the physician, it is not practicable to measure accurately by study of X-ray films previously obtained, the degree of dilatation of each chamber, or to make allowances for changes that may have occurred in the few days before death and after cardiograms were recorded.

Individual observers vary in their assessment of the degree of dilatation of the heart chambers in any one case. The maximal thickness of the free ventricular wall can be measured with accuracy, and by careful dissection the contribution of each ventricle to the septum can be determined by weighing. A comparison of heart weights in patients with similar thicknesses of ventricular walls shows, in this series, that the factor of dilatation must be very important. Unfortunately observations are not recorded by different pathologists in a uniform manner and are not always sufficiently precise. For example, one measurement of average ventricular thickness is usually made on each side. In fact ventricular thickness varies considerably from apex to base and the various chest electrodes are clearly placed over ventricular thickness of varying degree. Hypertrophied papillary and trabecular muscles sometimes interfere with accurate measurement of the thickness of the free wall of the ventricle, and the former probably have a definite influence on the cardiographic pattern of ventricular hypertrophy (Kossman *et al.*, 1948).

There is no doubt that the right ventricular patterns accepted do, in fact, reflect anatomical hypertrophy, but the principal problem lies in the large group of patients who have R.V.H. but show no electrocardiographic sign of this. The precise mechanism responsible for the cardiographic changes is unknown. It is difficult to accept the suggestion that they can be related solely to

changes in the position of the heart resulting from hypertrophy, and it is certain that they are not in direct proportion to the thickness of the ventricular wall beneath the exploring electrode. It may be that hypertrophy of the muscle fibres in the earlier stages does not materially increase the thickness of the ventricular wall but may yet affect the changes in electrical potential responsible for the electrocardiographic pattern. The mechanism by which dilatation affects the cardiogram and produces the so-called " strain pattern " is likewise not known, nor is it clear how rheumatic myocarditis affects the development of the hypertrophy pattern.

All these considerations make it quite impossible accurately to compare pathological and electrocardiographic findings. Nevertheless it can usually be decided whether R.V.H. does or does not exist and its approximate severity.

Biventricular Hypertrophy

From studying published papers and our own material we consider that biventricular hypertrophy may be diagnosed when (1) there are signs of L.V.H. *and* of R.V.H., a combination that is said to be unusual but was found in 4 of our patients, or (2) signs of L.V.H. and of pronounced clockwise rotation, as shown by R>Q in aVR and S>R in V5 and with inversion of T in V1.

Signs of L.V.H. with a vertical position of the heart are considered highly suggestive of combined hypertrophy. Signs of L.V.H. with inversion of T wave in V1 are considered suggestive, and with inversion of T wave in V1 and V2 very suggestive, of combined hypertrophy. Electrocardiographic signs of R.V.H. with a horizontal heart can occur in the absence of L.V.H. This combination of signs does not indicate biventricular hypertrophy and we have one case illustrating this point.

In the operation series, predominant mitral incompetence was present in 23 cases, aortic incompetence in 60, aortic stenosis in 3, and diastolic hypertension (B.P.>160/100) in 15, but in only 4 cases were there electrocardiographic signs of biventricular hypertrophy.

In the post-mortem series there were 22 cases with anatomical hypertrophy of both ventricles. In 11 of these the cardiographic signs were of isolated R.V.H. and in 2 of isolated L.V.H., but 6 did not show cardiographic signs of ventricular hypertrophy, and only 3 showed signs of biventricular hypertrophy. A detailed analysis of this material shows that considerable anatomical biventricular hypertrophy can occur in association with cardiograms showing R.V.H. alone or without evidence of R.V.H. or L.V.H. In two cases with L.V.H. signs alone in the cardiogram the anatomical L.V.H. was proportionately greater than the R.V.H., and the former seemed to be masking the cardiographic signs of R.V.H. It is probable that from the electrical point of view the signs of R.V.H. and of L.V.H. frequently balance each other and consequently no ventricular hypertrophy signs appear in the cardiogram. However, our cases indicate that there is no obvious relationship between the degree of hypertrophy in each ventricle and the presence or degree of cardiographic signs of biventricular hypertrophy.

It is concluded that electrocardiographic signs of combined ventricular hypertrophy are uncommon in patients with rheumatic heart disease, even though pathological examination shows that such hypertrophy may be considerable. From a practical point of view, in differential diagnosis of the relative importance of mitral stenosis and of mitral incompetence when both defects are present, electrocardiographic evidence of biventricular hypertrophy signifies that the degree of mitral incompetence is such that thoracotomy with a view to undertaking mitral valvotomy is not advisable. Predominant mitral incompetence associated with a high pulmonary vascular resistance and direct cardiographic signs of R.V.H. is uncommon. In relation to the problem of mitral stenosis associated with aortic valvular disease, the severity of the latter must be assessed on the signs in the peripheral arteries, and of the former on evidence pointing to substantial pulmonary hypertension in the absence of left ventricular failure. Cardiac catheterization may provide decisive evidence in favour of predominant mitral disease by revealing considerable pulmonary hypertension. Biventricular hypertrophy in the cardiogram due to associated aortic valvular disease is not necessarily a contra-indication to mitral valvotomy, because right mitral stenosis may be present.

Left Ventricular Hypertrophy

We have not made a definitive study of L.V.H. in rheumatic heart disease. The recognition of L.V.H. in patients with signs of mitral stenosis who are under consideration for surgical treatment is however very important because it invariably means that some significant complication is present. An accepted pattern of L.V.H. used to be left axis deviation in the standard limb leads with depression of the S–T segment and a low or negative T wave in lead I and such a pattern certainly points to the need for a more complete cardiographic study. Since the introduction of unipolar præcordial leads there is general agreement that the pattern of a tall R wave with depression of the S–T segment and a low or negative T wave in leads recorded over the left ventricle is a more reliable indication of L.V.H.

It is, however, difficult to be sure of absolute values for the height of R as explained (see page 468) and digitalis frequently affects the ST–T segment, the changes persisting for some weeks after administration has ceased. Sokolow and Lyon (1949) accept the following as absolute criteria for the diagnosis of L.V.H. in V5 or V6: (*a*) voltage of R>26 mm.; (*b*) depression of S–T segment > 0·5 mm.; (*c*) a flat, diphasic, or inverted T with a normal R and small S and S–T depression>0·5 mm.; (*d*) V.A.T.=0·06 sec. or more, especially when associated with a tall R wave.

Our findings are similar to those of Leatham in that the amplitude of R over the left ventricle in health may be more than 26 mm. There is room for further study on large numbers of cases but we consider there is usually a much wider variation in the height of R over the left than over the right ventricle and consequently an absolute standard cannot be reached.

Mitral Incompetence. When the physical signs of associated mitral stenosis and incompetence are accompanied by cardiographic signs of L.V.H. this signifies that the incompetence is predominant and the patient unsuitable for valvotomy, if aortic valvular disease and systemic hypertension can be excluded as important factors. There has been no exception to this rule. Free mitral incompetence may, however, occur with normal cardiograms even when there is clinical and radiological evidence of left ventricular enlargement.

Aortic Valvular Disease and Systemic Hypertension. Electrocardiographic evidence of L.V.H. from aortic stenosis or incompetence or from systemic hypertension is not in itself a contra-indication to mitral valvotomy, if other evidence points to severe mitral stenosis being present in addition.

Ischæmic Patterns

In some patients, transient S–T depression and flattening of the T wave has been observed during an attack of pulmonary œdema induced by tachycardia secondary to the emotion of examination for possible operation or from the exertion of coming up to hospital (Fig. 15). On occasion similar changes have been induced by an exercise test undertaken to try and determine the nature of a complaint of pain in the chest in a patient with mitral stenosis. In none of these patients was digitalis a possible factor in the genesis of the ST–T changes. Pain did not accompany any of the incidents during which these cardiographic changes were recorded. The cardiographic patterns differed from those of "ventricular strain" in that S–T depression of abnormal degree was the prominent change, whereas in the latter, the cardinal feature is T inversions often without any ST–T shift. Furthermore S–T depressions were not confined to right ventricular leads. In the strain pattern the T inversions occur only over the right ventricle.

In a patient with severe mitral disease and tachycardia and acute pulmonary œdema, coronary blood flow may be inadequate for muscle requirements during the episode and the electrocardiographic changes resemble those seen in the left ventricular chest leads during exercise or during an attack of angina pectoris in patients with coronary artery disease.

The Practical Value of Electrocardiography in the Assessment of Patients for Valvotomy

Just as absolute reliance can rarely be placed on a single physical sign, so in regard to special methods of investigation there are few absolute rules. Nevertheless, we consider that the cardio-

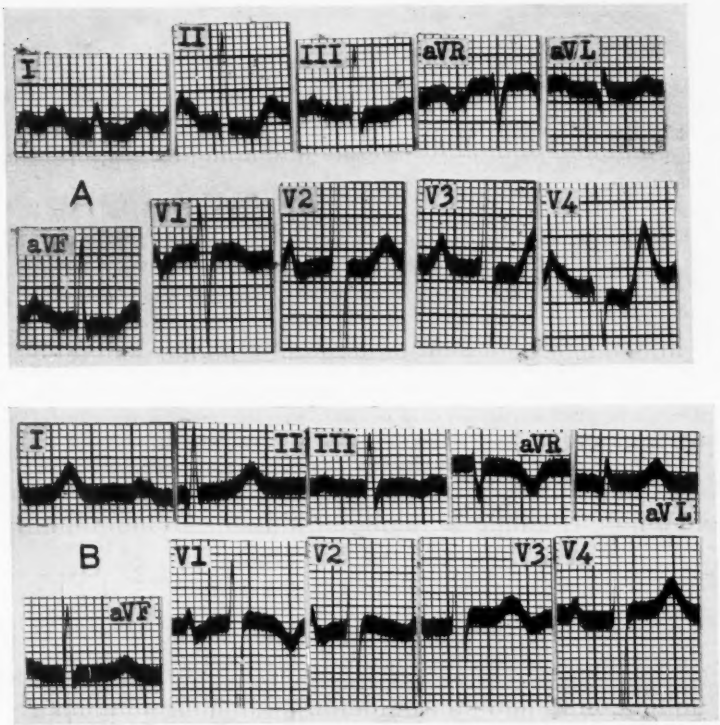


FIG. 15.—(A) Recorded during an attack of acute pulmonary œdema, showing S–T depression in I, II, VF, V2, V3, V4. (B) Recorded a day later, showing disappearance of S–T changes, the pattern being the same as that recorded before the pulmonary œdema developed.

gram may give useful information in the assessment of patients with rheumatic valvular disease especially in relation to operative treatment. The finding of an entirely normal cardiogram suggests that symptoms may be out of proportion to the real physical disability and if doubt exists on other grounds as to the necessity for operation cardiac catheterization may give useful guidance. Tight mitral stenosis may be associated with a normal electrical axis but the greater the degree of right axis deviation the more likely is R.V.H. to be present. Left axis deviation suggests that some significant complications may be present and other evidence for this should be sought.

In our experience, other things being equal, R.V.H. is a strong indication for considering surgical treatment because it usually signifies considerable pulmonary hypertension and a poor prognosis. Tight mitral stenosis is the usual cause but occasionally severe pulmonary hypertension is associated with predominant mitral incompetence and this possibility should be remembered and the other evidence reviewed with particular care.

The cardiogram may provide objective evidence of progression or regression of ventricular hypertrophy.

Signs of biventricular hypertrophy always mean that some important complication is present. L.V.H. from mitral incompetence is a contra-indication to operation for valvotomy but when due to associated aortic valvular disease severe mitral stenosis may be present in addition and the relative importance of each defect must be assessed on other grounds.

Cardiograms may be useful in recording an ischæmic pattern during an attack of dyspnœa or tachycardia and this finding constitutes an urgent need for valvotomy.

Summary and Conclusions

An electrocardiographic study of mitral valvular disease has been made in a series of 200 consecutive patients subjected to surgical treatment and in 38 post-mortem cases. In all detailed clinical radiological, and usually cardiac catheterization findings were available.

Standard and augmented unipolar limb leads together with leads V1–7 and CR1 were taken in the 200 operation cases and 36 of the 38 post-mortem cases. In addition, right-sided V leads were recorded in 141 of the operation cases. The following points were studied: axis deviation; the algebraical sum of R+S in lead I; the electrical position of the heart; P waves; Q–T and P–R intervals; absolute height of R and depth of S and the R/S ratio in the præcordial leads; Q waves; height of R and R/Q ratio in aVR; flattening or inversion of T and depression of S–T segment in præcordial leads; ventricular activation time; and the patterns of right bundle branch block.

The amount of useful information obtainable from the standard limb leads is limited. Although they do not provide a diagnostic pattern of R.V.H., indirect signs are frequently present and occasionally they provide the sole suggestive sign. Broad or bifid P waves of a type strongly suggesting mitral disease occurred in 92 per cent of the 115 patients in sinus rhythm. The duration of the QT*c* and P–R intervals did not provide reliable evidence of rheumatic activity.

The heart was vertical or semi-vertical in position in 90 per cent of patients with predominant mitral stenosis. When the heart was horizontal or semi-horizontal in position some factor complicating mitral stenosis was usually present.

Signs of R.V.H. were present in 89 per cent of cases with right axis deviation of 100° and in 100 per cent of cases in which the algebraical sum of R+S in lead I was negative by 3 or more, in 89 per cent in which R=3 mm. or more in aVR, in 89 per cent in which S=5 mm. or more in V5, and in 100 per cent in which R>Q in aVR or S>R in V5. Although changes indicating R.V.H. were commonly sought in V1, it is shown that sole or stronger evidence may be found in V2 or in the right-sided V leads (V3R, V4R, or VE). An absolute height of R>7 mm. in V1(2) or an R/S ratio>1 in leads recorded over the right ventricle almost certainly signifies R.V.H.

Complete or incomplete right bundle branch block, or a negative T in V1 and in V2 or CR1 are probably signs of R.V.H. in patients with rheumatic heart disease. The possibility of negative T waves resulting from myocardial fibrosis is discussed. A ventricular activation time>0·03 sec. is accepted as a sign of R.V.H. but in this series never occurred as a sole sign and is therefore of no practical value. Depression of the S–T segment may be found when other signs of R.V.H. are well marked. Transient depression may be due to ischæmia.

Electrocardiographic signs do not develop until the anatomical degree of R.V.H. is considerable. The relative importance of the various electrocardiographic signs of R.V.H. is discussed and reasons are given for concluding that in rheumatic heart disease it is not possible to grade the degrees of severity.

Brief reference is made to factors that influence the development of the R.V.H. pattern and difficulties in post-mortem studies are discussed. Justification for the electrocardiographic criteria of R.V.H. accepted rests on presumptive evidence based on clinical, radiological, and catheterization studies; regression of the various patterns following valvotomy and post-mortem correlation. Published criteria for the electrocardiographic diagnosis of R.V.H. are reviewed.

In this series an electrocardiographic diagnosis of R.V.H. was made in 115 of 176 patients (65%) in whom the presence of predominant mitral stenosis was confirmed at operation and in one patient with predominant incompetence. The detection of the electrocardiographic pattern for R.V.H. is important because it usually signifies that there is considerable pulmonary hypertension and that unless improvement can be obtained by operation the outlook is poor. In the great majority of cases of rheumatic heart disease, R.V.H. is secondary to tight mitral stenosis but occasionally when

pulmonary resistance is high R.V.H. may be found in association with predominant mitral incompetence.

Evidence of pre-operative progression or post-operative regression of R.V.H. may be recorded.

Criteria for the diagnosis of biventricular hypertrophy are discussed and it is concluded that cardiographic evidence of combined hypertrophy is important although uncommon even when anatomical bi-hypertrophy is considerable. When due to mitral incompetence, valvotomy for associated stenosis is not indicated but when due to aortic valvular disease or to systemic hypertension signs of biventricular hypertrophy do not necessarily indicate that tight mitral stenosis is not present in addition. Signs of L.V.H. invariably mean some important complication is present but likewise do not exclude the existence of severe mitral stenosis.

Finally, it must be concluded that there is no absolute electrocardiographic sign of R.V.H. because occasionally exceptions have been found or recorded for every criterion.

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A CASE OF TAKAYASHU'S SYNDROME: THE PULSELESS DISEASE

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The Takayashu disease (or pulseless disease according to Anglo-Saxon authors) is universally considered as an exceptional clinical rarity, worthy of detailed study and of being placed on record. Thus an addition to the small group of cases so far reported throughout the world may represent an important step towards the better knowledge of this most unusual ischæmic syndrome. The instance of Takayashu disease that we now recount possesses all the characteristics of that malady and presents, at the same time, some new features worthy of comment.

The most striking feature of the disease is the complete absence of arterial pulsation in the main arterial trunks arising from the aortic arch. It was first described by the Japanese ophthalmologist Takayashu (1908) whose attention was drawn to the serious ocular accompaniments that inevitably develop. From 1908 till the present time Japanese authors have described a total of 58 cases, which have been previously brought together by Caccamise and Whitman (1952) in a comprehensive survey of the pulseless disease.

Very few cases have been reported from other sources. However, two important reviews of those observed in Europe have lately been published by Skipper and Flint (1952) and by Ask-Upmark (1954). These authors concur in noting the actual and relative infrequency of the disease in the white race, although they do not entirely agree as to the total number of cases recorded. A critical study comprising some other cases not hitherto reported has been published by Anton Garrido and Ramirez Guedes (1953). Finally our very typical case is now added, making a total of 37 non-Japanese cases. It should, however, be noted that some few of the recorded cases do not fulfil the strict criteria necessary for the diagnosis to be established beyond doubt.

Case Report

An unmarried woman, aged 19, was admitted to hospital on June 30, 1953. She had been able to work in the household and on the farm. There was no significant family or past personal history. She was of asthenic constitution. Weight 48 kg., height 1·46 m.; menses irregular.

At the age of 18 she had aural vertigo and some short syncopal attacks with slight convulsions. She was complaining of progressive weakness and had noticed undue muscular tiredness in both arms, so that she was apt to drop things; this symptom was of the nature of intermittent claudication of the arms. In 12 months there had been three bouts of transitory hemiparesis, lasting for about half an hour, accompanied by dysarthria. Abrupt movements of the head accentuated the giddiness and even provoked syncope. The patient presented an obvious hypersensitivity of the carotid sinus. She suffered from frequent pains in the head. A few weeks after the onset of the illness, ocular troubles set in with progressive blurring of vision. There was total loss of sight in the right eye two months before admission to hospital.

The clinical examination of the heart showed only an accentuation of the aortic second sound. The aorta showed increased pulsation but none could be felt in the carotid, axillary, brachial, or radial arteries. Oscillometry in the superior extremities showed a greatly reduced amplitude on both sides, while in the legs the blood pressure was 180/80 mm. Hg. The oscillometric index in both thighs was 3·5. Pulsation was normal in the femoral, posterior tibial, and dorsalis pedis arteries in both legs. The electrocardiogram at rest and after effort was normal. No abnormality was found in the veins. There was a slight decrease of skin temperature in both arms. No abnormal signs were found in the respiratory system and no septic foci were discovered. Examination of the alimentary and nervous systems gave negative results. There was slight bilateral hypoacusis.

The results of laboratory examinations were as follows. E.S.R.: 32 mm. in one hour. Erythrocytes: 3,870,000/cu. mm. Leucocyte count: 10,300, with normal differential count. Urine examination, no albumin or sugar. Wassermann reaction, negative. Blood sugar, 89 mg.; cholesterol, 134 mg.; plasma protein: 8·24 g.; albumin, 3·24 g.; globulin, 5·0 g.; in each case per 100 ml. The leucocytosis and increased E.S.R. persisted at subsequent examinations. Coagulation time, 3·5 minutes. Bleeding time, 1 minute. Ocular examination on 13/7/53 showed cataract in the right eye. In the left fundus the veins were overfilled and showed irregular dilatation. The discs were normal.

Ophthalmological examination (21/2/54). Anterior chamber: adhesions between the cornea and the iris causing obstruction to the flow of aqueous humour. There were extensive atrophic zones of the pigmentary layers and parenchyma in the peripheral part of the iris. The pupil was dilated and fixed. In the right eye there was a total cataract of a mother-of-pearl colour. In the left eye, the lens showed slight peripheral opacities in the equatorial zones and small peripheral and central punctiform opacities.

Fundus of the eye. In the right eye it was not possible to see the fundus on account of the cataract. In the left eye, irregular sinuous filaments and floating bodies were observed. These findings were most marked in the posterior region of the vitreous.

Retina and optic nerve: the retina showed a yellowish colour. The veins were tortuous and of a calibre larger than normal. Within, the blood flow could be observed, having the appearance of coffee grounds, and circulating slowly and irregularly. In the temporal zones there was seen an arteriovenous anastomosis in the form of a wide arch. In the superior peri-papillary portion of the retina there were small patches of whitish exudate, possibly remains of previous hæmorrhage.

The optic nerve was in process of atrophy, as was shown by its colour and the well defined cribriform lamella. The disc margins were irregular and indistinct. In the temporal portion there was a conspicuous accumulation of choroidal pigment. The visual acuity of the right eye was nil on account of the total cataract. In the left eye it was scarcely 1/10. The visual field was much reduced as a consequence of the optic nerve atrophy. Tension in the right eye was 50, in the left eye 20.

The assessment of the exceptional circulatory symptoms and signs and the peculiar features of the ocular disturbance combined to clinch the diagnosis of Takayashu disease. Throughout the year in which the patient has been under our clinical observation, there has been no change in the cardiovascular state. In a quiet environment and with avoidance of effort, there has been no repetition of the cerebral ischaemic episodes or the claudication of the superior extremities. The ocular disturbances have, on the other hand, become progressively worse. In the right eye, in which intraocular pressure was abnormally high, a malignant glaucoma developed necessitating the enucleation of the eye on 8/1/54. Subsequently the cataract in the left eye was removed in order to ameliorate, as far as possible, the serious defect of vision in that eye.

Morphological Examination of the Enucleated Eye. Sclera thin. No pathological products in the vitreous or in the chambers.

The microscopical examination revealed the presence of a connective vascular lamina, histologically of embryonic aspect, extending in front of the retina, with its greatest thickness at the level of the periphery of the papilla, becoming progressively thin peripherally, till it ends by a sharpened edge in the equatorial zone. In front of the papilla there exists a sort of truncated cone which at its vertex gets lost in the vitreous (Fig. 1). The conoid formation is not centred on the papilla but corresponds to an edge of it. It is formed by a very delicate fibrous connective tissue with blood vessels, very few cells and fine collagenous fibrils, with

abundant œdematous matrix. Towards the vertex of the " cone " the cellular density increases progressively, the cells being of two types, starred mesenchymal or fusiform and lymphoid cells, the former predominating. There were also some occasional isolated neutrophile granulocytes but without inflammatory foci or recent or old hæmorrhage. The vascular structure is very remarkable with dilated capillaries or venules with very fine walls (Fig. 1). Through the contour of the papilla the tissue proper of the " cone " extends in all directions before the retina, getting progressively thin in its advance till there finally appears a fine chink between it and the latter. The pellicle in question has the same structure as the suprapapillar cone, with predominance of the zones where the fundamental substance abounds; cells and fibrils are very scanty (Fig. 2 and 3).

FIG. 1.—Hyaloid " cone " on the papilla (somewhat peripheral side of it). Note large vessel with aneurysmal dilatations.

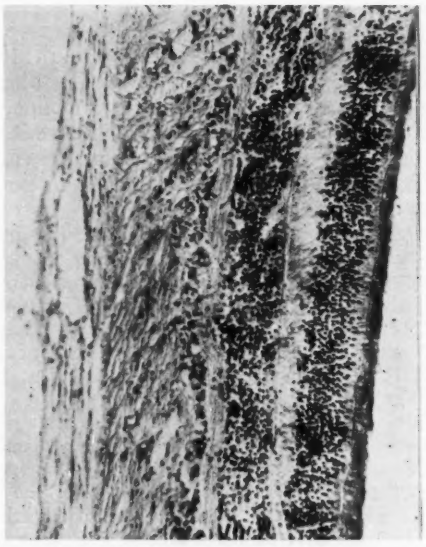

FIG. 2.—Disorganization of retina, with enlargement. Gliosis and rich vascularization of the layers of optic nerve fibres. Pre-retinal membrane with a large vein.

There is a cataract in the lens. The iris is atrophic. In the retina, apart from the lesions due to glaucoma, there are large calibre vessels sometimes with thick walls (especially of the arteries) in the nerve fibre layer, this condition being specific for this malady (Fig. 4). Neither lesions of the vascular walls nor thrombosis have been observed.

It is thought that the glaucoma has been provoked in this case by the synechiæ of the iris, being therefore a secondary glaucoma. However, it is noted that at the level of the irido-corneal angle there are not even vestiges of an earlier pathological process, which is important if we take into account the rapidity of the process. All the other lesions except the " pre-retinal membrane " of the " cone " may be attributable to the glaucoma. The " cone " and the membrane are therefore lesions peculiar to this disease, not hitherto described as far as we know.

No trace whatever of the hyaloid artery has been found nor cords resulting from its obliteration; nor are there indications of inflammation or hæmorrhage, old or recent, or other morbid process in the vitreous or the retina.

Have these ocular lesions any pathogenetic connection with the pulseless disease or are they in this case a pure coincidence with the fundamental process? The former hypothesis is supported by the evidence of mesenchymal derangements in the eye (the cone and its peripheral extension) and by the unusually large calibre of the retinal arteries.

FIG. 3.—Pre-retinal membrane highly enlarged. Notice a fine crevice between it and the retina.

FIG. 4.—Inner part of retina with a large calibre artery in the layer of optic nerve fibres, making a bow on the inner molecular layer. Groups of disintegrated ganglion cells, above and on either side of artery.

DISCUSSION

Among previously reported cases there are few that present the classical features of pulseless disease manifested in the present example. These may be grouped as follows.

Suppression of the Arterial Pulsation in the Upper Half of the Body. Complete bilateral abolition of arterial pulsation of the carotid, axillary and radial arteries.

Symptoms due to this Circulatory Insufficiency. Claudication provoked by minimal muscular effort of either arm, headache, syncopal crises in connection with a hypersensitivity of the carotid sinus, and occasionally convulsions that occur either spontaneously or on sudden change of posture of the head. There may also be transitory hemiparesis.

Ocular Anomalies. Structural defects in the retinal vessels, particularly in the veins, leading to papillary degeneration and to progressive blindness; aneurysmal dilatations and arterio-venous communications of retinal vessels and formation of bilateral cataracts. In our case, glaucoma necessitating the enucleation of the right eye developed as well.

Precocious Appearance of the Ischæmic Syndrome. This patient was aged nineteen years.

The diagnosis of the Takayashu's syndrome is based not only on the existence of ischæmic disturbances of unusual distribution, but also on the circumstance of its appearing in youth. If we consider that the pathological basis of the disease is an obliterating thrombo-arteritis of the large vessels that arise from the aortic arch, the discovery in some necropsies of an obliterating panarteritis affecting the initial portion of the big arterial trunks of the aortic arch has suggested an inflammatory process caused by infection. The peculiar morbid process has to be distinguished from arterial obliteration that may occur in adult life by reason of syphilitic infection or arteriosclerosis, and in young adults of both sexes through malignant hypertension and arteriosclerosis. The evidence in this case of congenital mesenchymal abnormalities in the enucleated eye (pellicle, cone) support the pathogenetic hypothesis of the disease as developing on a

dysontogeneto basis. Among the 58 cases published by Japanese workers, the age is known in 44; in 36 of these the illness began before the age of twenty-five. Among these 36 there were 33 females. Of the 39 cases reported from other countries than Japan, only 10 (including the present instance) began to suffer from the disease before the age of 25 and all of these were females. Griffin (1939) has described a case in which a woman of 19 years showed this ischæmic syndrome in conjunction with persistent ductus arteriosus. The example recorded by Elliot *et al.* (1939) presented a combination of ischæmic disorders causing syncopal attacks and congenital abnormality of those arteries usually affected in Takayashu's syndrome.

Summary

A case of Takayashu's syndrome (pulseless disease) has been described. The patient presented the classical features of this disorder comprising arterial disease of obliterative type involving the main trunks arising from the aorta in a woman aged 19. Absence of pulses and intermittent claudication in the arms, and syncopal attacks associated with carotid sinus sensitivity were the main cardiovascular symptoms.

Progressive and severe ocular disease leading to glaucoma and the ultimate enucleation of one eye was associated with the cardiovascular disease. These lesions occurring precociously in a young woman clinched the diagnosis. Mesenchymal abnormalities observed in the enucleated eye suggested a possible congenital basis for the disease.

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THE NORMAL AND ABNORMAL INTER-ATRIAL SEPTUM

BY

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This paper is an elementary study of the normal and abnormal inter-atrial septum and an attempt to clarify the nomenclature and classification of the various kinds of septa on embryological grounds.

During fœtal life, the left ventricle receives almost no blood from the lungs, and must therefore get it from the venæ cavæ via the common atrium, if it is to perform any work to help in its proper development. Herein lies the reason for the apparent complexity in the development of the inter-atrial septum because the septum must be so built that it will at all times in fœtal life allow blood to flow from right to left. Obviously a simple septum cannot do this, and the only solution is the natural one—the evolution of a one-way valvular partition, which allows the free flow of blood from right to left throughout fœtal life but can readily be closed by the rise of left atrial pressure that takes place at birth.

The simplest form of valve has two components, one fixed and the other moving. In the inter-atrial septum, the fixed component (or seating) is the thick septum secundum, and the moving component is the thin septum primum. In order that the valve shall open from right to left (and close in the reverse direction), the moving part must be on the left side of the fixed part, and so the septum primum forms to the left of the septum secundum.

Fig. 1 traces the evolution of the normal inter-atrial septum by means of cardboard models and sectional diagrams. Its understanding makes easier the study of the ostium primum and ostium secundum septal defects illustrated by models and photographs of actual specimens in Fig. 2.

Apart from ostium primum and secundum defects, which are readily explained, there is another type of defect, more difficult to interpret, which may be associated with abnormal pulmonary venous drainage. An example is shown in Fig. 3, and the possible embryology is discussed.

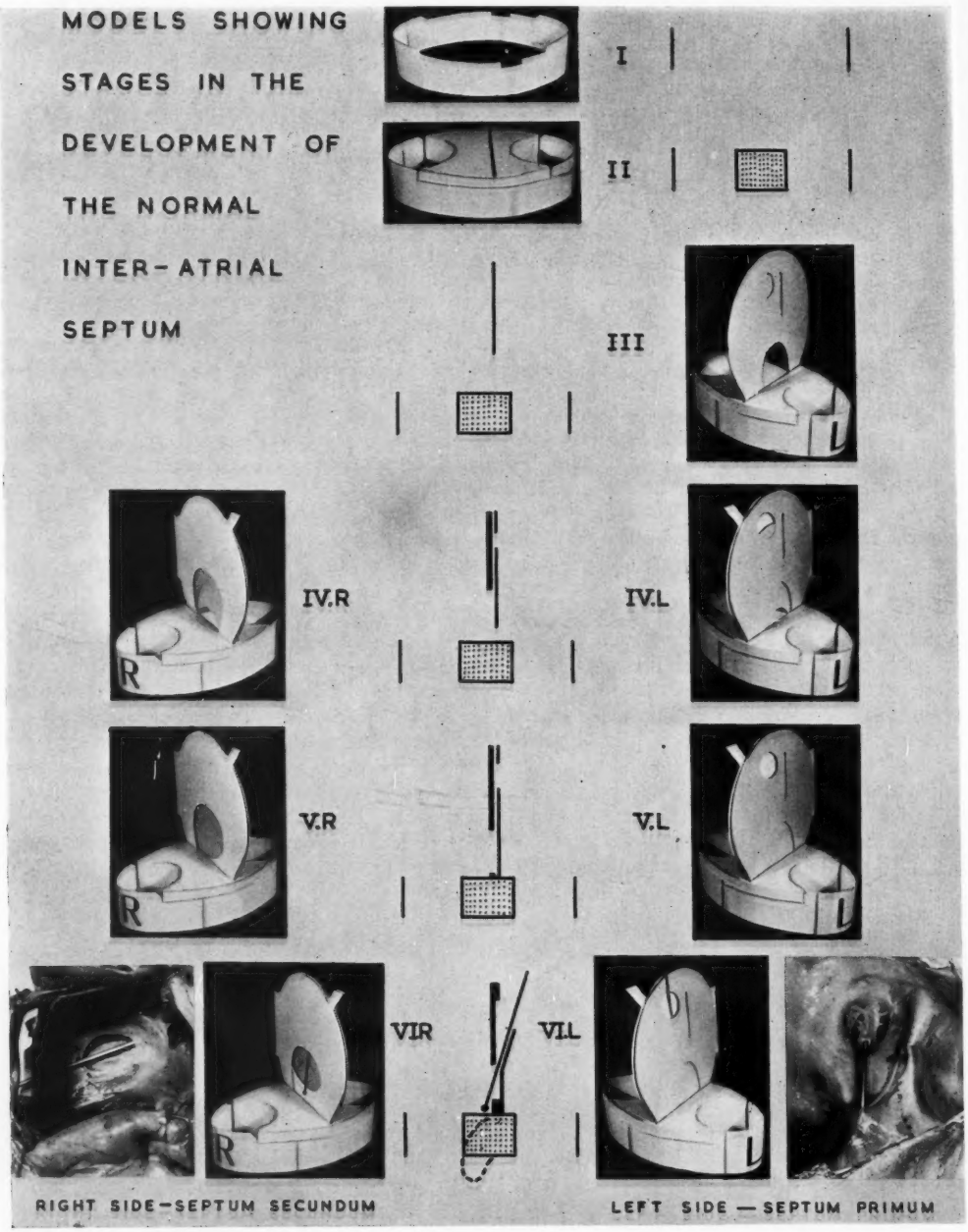
MODELS SHOWING STAGES IN THE DEVELOPMENT OF THE NORMAL INTER-ATRIAL SEPTUM
I
II
III
IV.R
IV.L
V.R
V.L
VI.R
VI.L
R
L
RIGHT SIDE—SEPTUM SECUNDUM
LEFT SIDE — SEPTUM PRIMUM

FIG. 1.

NORMAL DEVELOPMENT OF THE SEPTUM (FIG. 1)

I. The atrioventricular canal—the passage between the common atrium and ventricle.

II. The canal has been subdivided into mitral and tricuspid orifices by the union of endocardial cushions which grow towards each other from the front and back of the canal. The antero-posterior fissure indicates the site where the septa will meet the cushions.

III. The septum primum has appeared in the shape of a crescent—the aperture in its lower part is the ostium primum.

IV. L. and R. On the left side, the ostium primum is closing but at the same time a second aperture —the ostium secundum—is appearing by breakdown of the septum primum higher up. On the right side, the thicker septum secundum has appeared, at first being similar in appearance to the early septum primum. The broad and narrow projections indicate the positions of the inferior and superior venæ cavæ respectively.

V. L. and R. On the left side, the ostium primum is quite closed and the ostium secundum fully opened. On the right side the anterior limb of the septum secundum is growing across the base of the septum primum.

VI. L. and R. Completion of septum. On the left side, the septum primum is complete. On the right side, the anterior limb of the septum secundum has grown towards the inferior vena cava, so completing the foramen ovale, the thick margin of which is the annulus ovalis. The shallow fossa ovalis so formed is floored by septum primum.

The septum is now complete, and the septa partly stuck together, though blood can still flow into the foramen ovale and out from the ostium secundum as indicated by the knitting-needle. For comparison a typical example of this *valvular foramen ovale* is shown.

This state of affairs persists for several months after birth (though of course the valve is kept shut by the rise of pressure in the left atrium), and throughout life in about 15–20 per cent * of adults—the so-called patent foramen ovale. This is an ambiguous term since it implies that the foramen ovale may itself sometimes close up: this is very rare and it results in an imperforate interatrial septum and atresia of the left ventricle. In the remaining 80–85 per cent adults, the two septa become completely fused and the foramen ovale may be described as *sealed*. The sectional diagram indicates how the right portion of the fused endocardial cushions bends downwards to take part in the formation of the membranous part of the ventricular septum, the posterior part of which separates the right atrium from left ventricle.

* Author's own figure is 16 per cent of 100 adult hearts with normal inter-atrial septum.

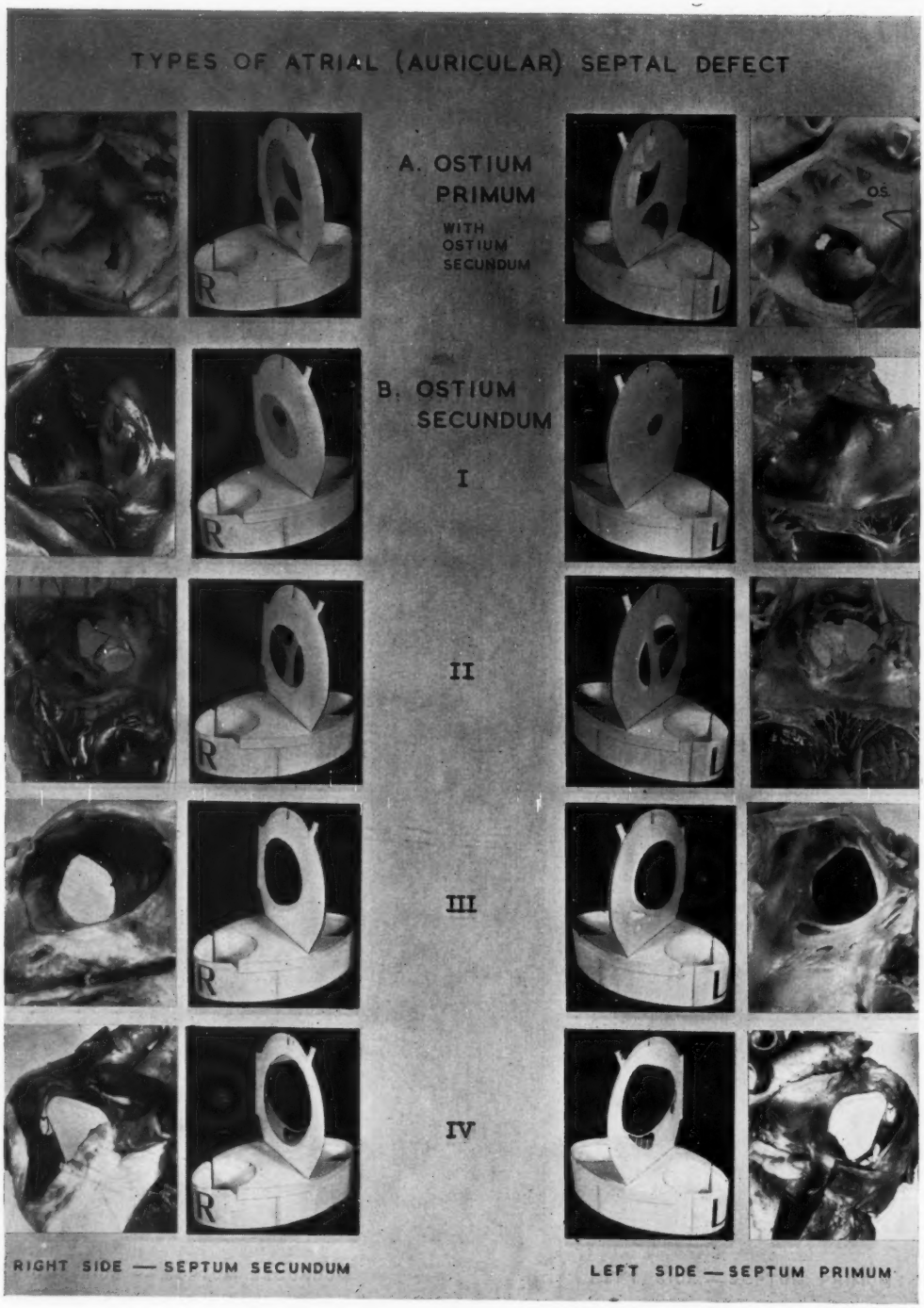
TYPES OF ATRIAL (AURICULAR) SEPTAL DEFECT
A. OSTIUM PRIMUM
WITH OSTIUM SECUNDUM
B. OSTIUM SECUNDUM
I
II
III
IV
OS.
R
L
RIGHT SIDE — SEPTUM SECUNDUM
LEFT SIDE — SEPTUM PRIMUM

FIG. 2.

TYPES OF ATRIAL SEPTAL DEFECT (FIG. 2)

An atrial septal defect is a permanent two-way communication between the right and left atria and it may arise in two main ways.

(1) When the septum primum and septum secundum do not completely overlap the ostium or ostia in each other (A and B and Fig. 2, A and B.)

(2) In association with abnormal pulmonary venous drainage (C and Fig. 3.)

A. Ostium Primum Defect

In the example illustrated, on the left side, the ostium primum has persisted, and above it, the septum primum has broken down into several holes (ostium secundum). On the right side, the septum secundum has also failed to develop across the ostium primum in the base of the septum primum, and has also left uncovered part of the ostium secundum, so this specimen shows both ostium primum and ostium secundum defects.

The tricuspid valve can be seen from the *left* atrium as well as from the right.

If the septum secundum had grown further down (or the ostium secundum appeared higher up), there would have been an ostium primum only, though the ostium secundum opening might have become valvular.

B. Ostium Secundum Defect

In this, the ostium secundum lies partially or completely in the same area as the foramen ovale. Four examples, in order of size, are illustrated.

I. From a case of congenital pulmonary valve stenosis. On the left side is a small ostium secundum which on the right side is seen to lie in the floor of a shallow fossa ovalis.

II. On the left side the ostium secundum is much larger but is still bridged by some ribbons of septum primum. On the right side, the foramen ovale is roughly the same size as the ostium secundum, and through it can be seen the strips of septum primum which bridge the ostium secundum.

III. On the left side the septum primum has broken down even further, resulting in one large ostium secundum with one or two smaller ostia nearby. On the right side the foramen ovale almost exactly corresponds with the ostium secundum.

IV. On the left side there has been almost complete breakdown of the septum primum, though around the periphery are some fenestrated remnants. On the right side is a huge foramen ovale, even larger than the main ostium secundum. This example represents virtually a single atrium.

C. Defect Associated with Abnormal Development of the Pulmonary Venous Drainage

In the normal heart, the pulmonary veins open into that part of the left atrium known as the vestibule. Keith (1948) states that it is highly probable that in the human the vestibule of the left atrium is a leftward extension of the sinus venosus, as in amphibians. This extension towards the left side of the common atrium normally becomes cut off from the main sinus venosus in the human by the inter-atrial septum so that the pulmonary veins come to open into (the vestibule of) the left atrium.

In fishes, the " pulmonary vein " (from the swim bladder) enters the sinus venosus. In man, if the pulmonary veins enter the sinus venosus, they will come to open into the right atrium since the sinus venosus becomes incorporated into the right atrium, being roughly that part of the posterior wall between the venæ cavæ and the coronary sinus. It is worth noting in passing that the pulmonary veins have also been recorded in man as entering the right and left ducts of Cuvier or their terminations, the right and left horns of the sinus venosus. The left duct and horn form the left superior vena cava (which usually survives only as the tiny vein of Marshall) and the coronary sinus. The right duct and horn form the part of the right superior vena cava below the azygos vein.

Now if some of the pulmonary veins enter the main sinus venosus, and the others enter the leftward extension of the main sinus which forms the vestibule of the left atrium, and if this extension *maintains its communication* with the main sinus, then some pulmonary veins will come to open into the right atrium, and the remainder into the vestibule of the left atrium (as normally) and there will be an interatrial septal defect where the main sinus and its extension communicate.

In the example shown in Fig. 3, on the left side can be seen an ostium secundum defect (O.S.),

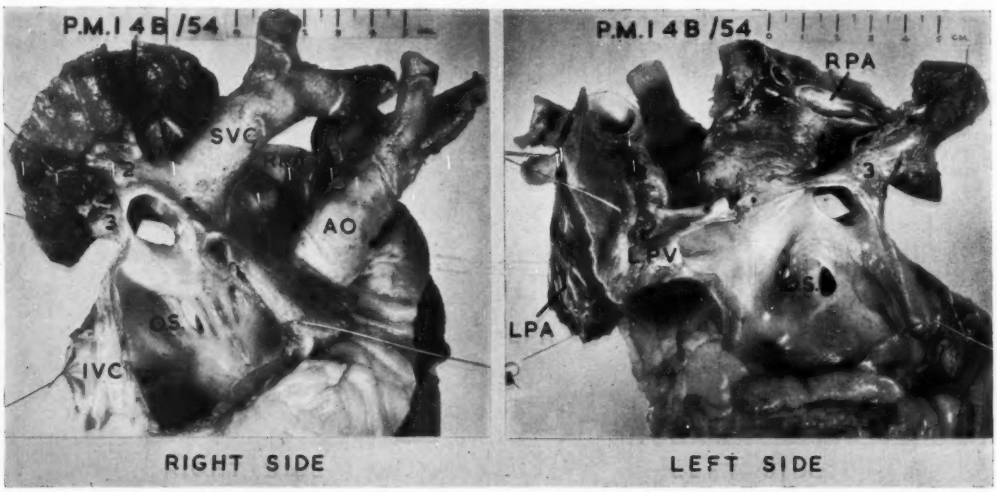

FIG. 3.

but above it is a much larger septal defect, to the left atrial side of which the lower right pulmonary vein (3) opens. The left pulmonary veins (LPV) enter normally. Note the complete occlusion of both main pulmonary arteries (LPA and RPA) by thrombus—a not uncommon complication of atrial septal defect.

On the right side is the small ostium secundum defect (O.S.) in the antero-superior part of the fossa ovalis. Above this is the larger septal defect to the right atrial side of which opens the superior vena cava (SVC) and the upper two main right pulmonary veins (1, 2). The lower right pulmonary

vein (3) opens mainly into the left atrium. The right main pulmonary artery (RPA) is shown opened and filled with thrombus. IVC is the inferior vena cava and AO the aorta.

The large septal defect may therefore be a persistence of the communication between the main sinus venosus (which incorporates into the right atrium into which the upper right pulmonary veins have come to open) and its leftward extension which forms the vestibule of the left atrium (into which enter all the left pulmonary veins and the lower right pulmonary vein).

Classification

On the basis of the above account the following classification of the inter-atrial septum is suggested.

Normal Septum—Septa overlapping each other's ostium completely.

Foramen ovale .. .. .. —valvular (unsealed)
—sealed

Abnormal Septum—Atrial (Auricular) Septal Defect

A and B. Septa not overlapping each other's ostium or ostia completely.

A. Ostium primum .. .. —alone
—with ostium secundum (example illustrated)
—with valvular "foramen ovale" (as described by Bedford, Papp, and Parkinson, 1941).

B. Ostium secundum .. (4 examples illustrated).

C. Associated with abnormal pulmonary venous drainage. This defect may be accompanied by another defect elsewhere in the septum such as an ostium secundum defect, as in the example shown (Fig. 3).

Summary

An illustrated account is given of the development of the normal inter-atrial septum, and of various forms of atrial septal defect resulting either from failure of septum primum and septum secundum to cover each other's ostium or ostia, or from the development of an abnormal pulmonary venous drainage. Finally a simple classification is suggested based on modern embryological nomenclature.

I should like to express my thanks to Mrs. O. Connolly for her help with the photography.

Part of this paper was demonstrated during 1954 to the British Cardiac Society in Cambridge, the Pathological Society of Great Britain in Edinburgh, and to the Society of Thoracic Surgeons in London.

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SPATIAL VECTORS AND THE ANGLES THEY ENCLOSE

BY

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The spatial vector and loop allow a more concise description of the heart's total electromotive force at an instant, and throughout the cardiac cycle, than the conventional electrocardiogram and the three-plane vectorcardiogram.

The magnitude of spatial vectors and the angles enclosed by these vectors are independent of cardiac position. Their relationship to the cardiac forces is therefore relatively simple. This suggests a promising new approach to the hitherto unrewarding quantitative analysis of the electrocardiogram.

With all lead-systems now in common use, the accuracy of quantitative measurement is limited by the errors inherent in Einthoven's hypothesis. These errors are augmented especially with regard to the sagittal component, where vectors are by-products of unipolar chest lead recording as with the ingenious mechanical models of Langner (1952), Urschel and Denton (1952), and Simonson and Ross (1953), and with the electronic method of Donzelot *et al.* (1950). The phase-shift error, introduced by recording leads separately with a single-channel instrument, is regarded as significant by Holzmann (1945, p. 58) and Burch *et al.* (1953), and as unimportant by Goldberger (1953).

In the present study the frontal lead-pair Y, X and the coronal pair Z, X of the " cube " lead arrangement, were recorded with a two-channel electrocardiograph. The technique of recording has been described (Fischmann and Brown, 1954). Spatial vectors have been determined by correlating frontal and coronal lead-pairs. Lead X, which appears in both lead-pairs, is used to identify synchronous points in the two records.

NON-QUANTITATIVE METHOD OF ANALYSIS

The orientation of the spatial QRS loop is that of its longest vector. In the scalar component lead record, the peak of the greatest QRS deflection (Q*y* in Fig. 2A; Q*z* in Fig. 2B; R′*y* in Fig. 2C) marks the instant corresponding to this vector (Fischmann and Brown, 1954). Consideration of *x*, *y*, and *z* (voltages in leads X, Y, and Z) at this instant, will give the general orientation of the longest spatial QRS vector. As shown in Fig. 1, positive deflections in lead X mean left-, in lead Y head-, in lead Z forward orientation of the instantaneous vector. Thus for instance in Fig. 2A the longest QRS vector is foot- (Q*y*), left- (R*x*), and forward (R*z*) orientated. The order of enumeration indicates the relative size of the three components. The small initial r or q, and terminal r′ or s deflections in leads X, Y, and Z can be similarly employed to determine the spatial orientation of initial and terminal vectors; *x*, *y*, *z* corresponding to the peak of the greatest T wave, the orientation of the T loop. Records from a normal subject, and from subjects with left and right ventricular hypertrophy, are shown in Fig. 2, and analysed in the legend.

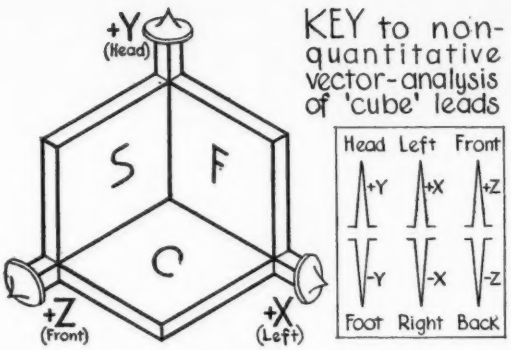

FIG. 1.—Polarity of the three leads (Y, X, Z) of the "cube" lead arrangement. F frontal, C coronal, S sagittal planes, defined by the axes of these leads. Left anterior oblique view. The three leads have a common zero point (the right lumbar electrode). Vectors directed *away* from this point give a positive deflection in the corresponding lead. Thus (inset) positive deflections in leads Y, X, and Z mean headward, left, and forward directed vectors respectively; and negative deflections mean opposite vector directions as shown.

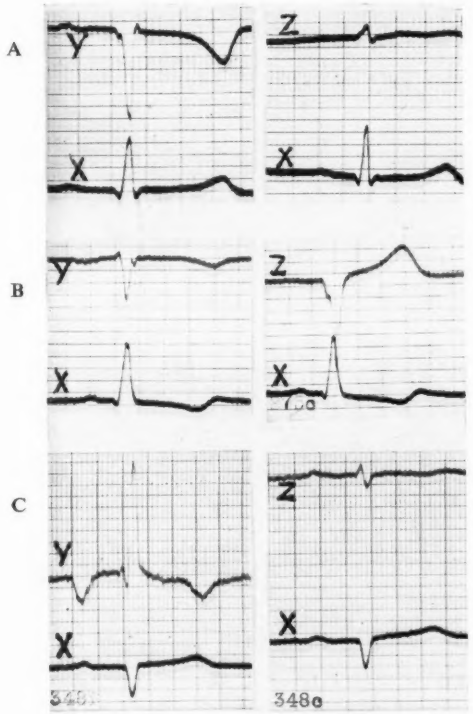

FIG. 2.—The spatial orientation of QRS and T loop, i.e. of longest QRS and T vector, by simple inspection of frontal and coronal lead-pairs. Non-quantitative method. X transverse, Y caudo-cranial, Z sagittal lead. Time marks 1/10 and 1/50 sec. Calibration 1 mV =1·5 cm. (A) *Normal heart*. The nadir of greatest deflection Q*y* (footward) marks the instant of the longest QRS vector. Synchronously with the latter, lead X shows positive (leftward), lead Z slightly negative (backward) voltage. The longest QRS vector is thus footward, left, and backward orientated; the order of enumeration shows the relative size of the three components. T ($-y$, x, z) is footward, left, and forward. (B) *Left ventricular hypertrophy*. Synchronously with greatest deflection Q*z* (backward), lead X shows positive (left), lead Y negative (footward) voltage: backward, left, footward orientated QRS loop. T (z, $-x$, $-y$) is forward, right, footward. (C) *Right ventricular hypertrophy*, right bundle branch block. Synchronously with peak of greatest deflection R′*y* (headward), lead X shows negative (right), lead Z also negative (backward) voltage: headward, right, backward QRS loop. T ($-y$, x, z) is footward, left, forward.

QUANTITATIVE METHOD OF ANALYSIS

Vector Summation of Three Components. At any instant the voltages x, y, and z in leads X, Y, and Z are transverse, caudo-cranial, and sagittal components of the spatial cardiac vector Esp.

$$\text{Esp}=x+y+z \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The vector sum of x, y, and z can be obtained by setting y off from the end of x, then setting z off from the end of y, and connecting free onset with free end (Henrici and Turner, 1903; Rutherford,

1951). In keeping with the "law of commutation," components may be drawn in any desired order. Thus in Fig. 3A x follows z, and y follows x. It is not possible to perform the summation of three non-coplanar components, without transformation into coplanar pairs. Transformation is easily achieved if in equation (1) $x+y$ is replaced by Ef, or $x+z$ by Ec, or $y+z$ by Es; where Ef, Ec, and Es are frontal, coronal, and sagittal instantaneous vectors. Equation (1) can then be re-written as follows:

$$\text{Esp}=\text{Ef}+z=\text{Ec}+y=\text{Es}+x \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

This is to say that *at any instant the spatial cardiac vector is the vector sum of a plane vector and of the voltage in the non-coplanar component lead.* The sum of Ec and y is used in the present study. Each spatial vector is determined in two stages, expressed by the equations $x+z=\text{Ec}$ and $\text{Ec}+y=\text{Esp}$. All terms of equation $x+z=\text{Ec}$ are in the coronal plane (Fig. 3B); those of equation $\text{Ec}+y=\text{Esp}$, in a plane which is perpendicular to the coronal and intersects the latter plane in a line corresponding to the coronal vector (Fig. 3C).

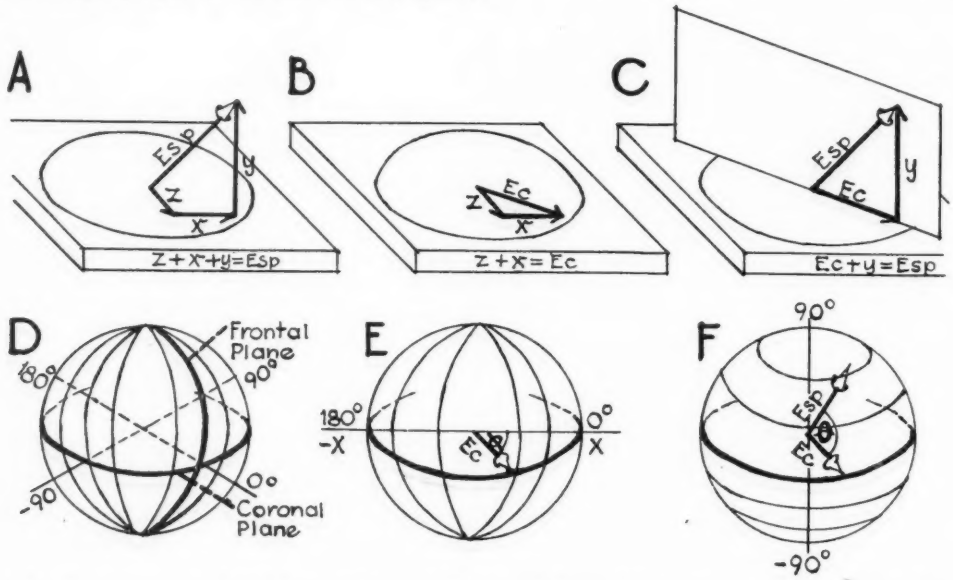

FIG. 3.—The vector summation of three components. Ec coronal, Esp spatial vector; x, y, z instantaneous voltages in leads X, Y, Z; ϕ longitude, θ latitude angle. (A) Esp as the vector sum $z+x+y$: x set off from end of z; y set off from end of x; Esp connects free onset with free end. (B and C) Esp obtained by two coplanar summations: (B) x set off from end of z, Ec connects free onset with free end. (C) y set off from end of Ec, Esp connects free onset with free end. (D) Spatial coordinate system. (E) Ec and the X axis enclose longitude angle. (F) Esp and Ec enclose latitude angle.

Spatial Coordinate System. The direction of frontal, coronal, and sagittal plane vectors can be stated in terms of a circular scale, such as Einthoven's, if all vectors in the plane are drawn to commence from the centre of the scale. In the present study this type of representation has been extended as follows: the direction of any spatial vector commencing at the centre of a sphere can be indicated by marking a point on the sphere's surface. To be able to state the position of such points, a coordinate network will have to be drawn on the sphere. The earth's longitude–latitude network was chosen for this purpose (Fig. 3D). It has the advantage of being well known and easily visualized. The coronal plane was laid through the equator, the frontal plane through the 0° longitude great circle, of the globe. "Viewing" the coronal plane from below, the negative

angles of the Einthoven scale in that plane are disposed anteriorly. Longitude, ranging from 0° to 180°, was therefore called negative on the anterior, positive on the posterior hemisphere. Latitude ranged from 0° at the equatorial circle, headward to 90°, and footward to −90°. The angle ϕ, enclosed by Ec and the X axis, is identical with the longitude (Fig. 3E), and the angle θ, enclosed by Ec and Esp with the latitude (Fig. 3F), of the spatial vector.

Construction of Spatial Vectors. The two vector summations $z+x$ and Ec$+y$ can be carried out on the ECG strip (Fig. 4). As an alternative method a biaxial chart (Fischmann and Brown, 1954 (Fig. 2)) may be used for the summation of x and y; whilst Fig. 5 of the present paper was employed for the summation of Ec and y.

The Angle Enclosed by Two Spatial Vectors. The significance of the QRS–T angle was shown by Grant *et al.* (1951), further studied on mechanical vector models by Langner (1952), Urschel and Denton (1952), and Simonson and Ross (1953) and, with the aid of trigonometric tables by

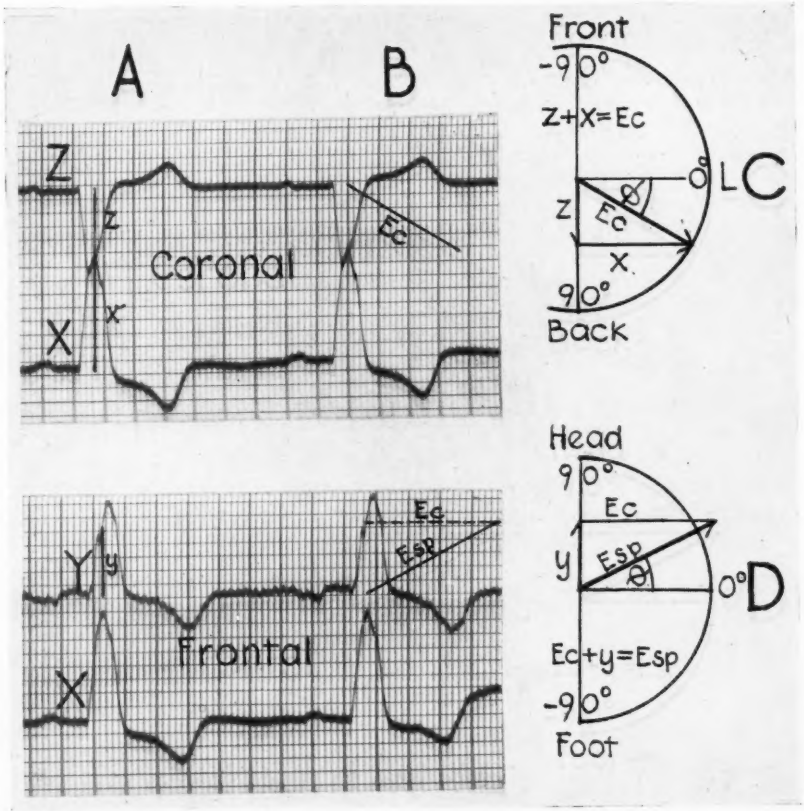

FIG. 4.—Construction of a spatial instantaneous vector on the ECG strip. Quantitative method. Abbreviations as Fig. 3. (A) x, y, and z at an instant corresponding to peak of Rx. (B) On the coronal lead strip x is set off from the end of z. Ec connects free onset with free end. Ec is then transferred to frontal lead-pair, and set off from the end of y. Esp connects free onset with free end. Longitude is the angle enclosed by Ec and the horizontal; latitude the angle enclosed by Esp and the horizontal. (C) and (D) Graphic representation of these operations. Time marks 1/10 and 1/50 sec. Calibration 1 mV=1·5 cm.

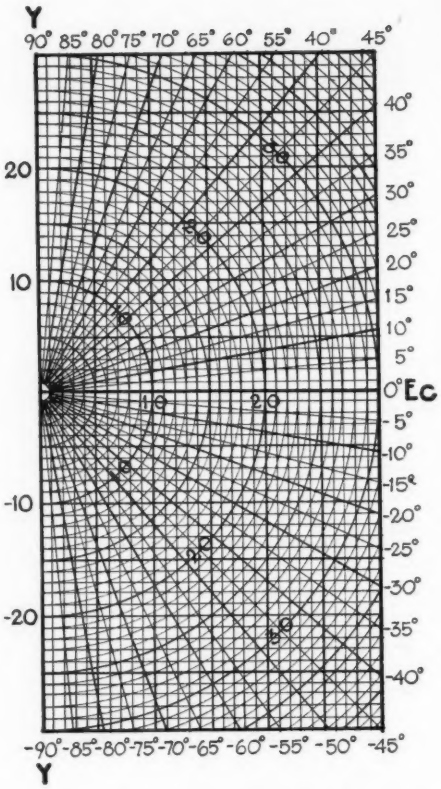

FIG. 5.—Biaxial chart for the summation of the coronal vector Ec, and the non-coplanar lead voltage *y* (modified after Wenkebach and Winterberg). The concentric semicircles divide the radii of the figure, including the vertical axis Y (representing the axis of the caudo-cranial lead) and the horizontal axis (representing the coronal vector), into ECG amplitude mm.

The terminus of Ec is marked on the horizontal axis. The vertical line passing through the terminus of Ec is then followed upward if positive, and downward if negative, to a point corresponding to the magnitude of *y*; this point is the terminus of the spatial vector Esp. The magnitude of Esp is read on the scale formed by the concentric circles; the latitude angle read at the border of the chart.

Helm and Fowler (1953). The angle enclosed by two vectors can be measured rapidly and simply, on a " blackboard " terrestrial globe showing the longitude–latitude network without the earth's map. Two chalk marks, corresponding to the two vectors, are made on the globe (Fig. 6A). The

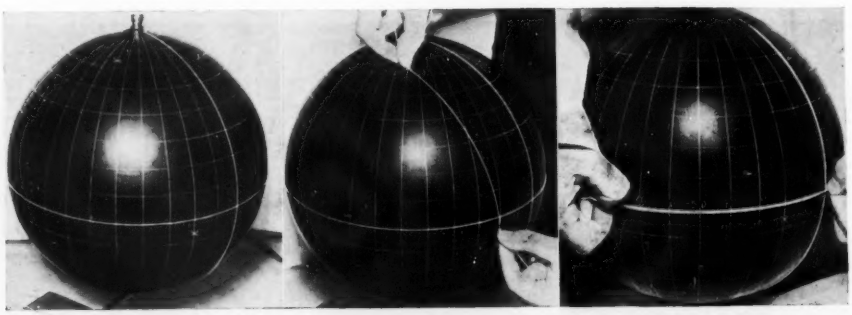

FIG. 6.—Measurement of the angle enclosed by two spatial vectors. (A) The two chalk crosses on the blackboard globe correspond to two spatial vectors. (B) The shortest distance between the two marks is measured with a cotton thread. (C) The angle enclosed by the two vectors is read after placing the thread along the equator of the globe.

shortest distance between the two marks on the globe's surface is then measured with a cotton thread (Fig. 6B). If the thread is placed on the equator, the angle enclosed by the two vectors can be directly read (Fig. 6C).

Single-curve Vectorcardiogram. If points corresponding to consecutive vectors of a cardiac cycle were marked on the surface of the globe, the curve connecting these points would indicate the direction but not the magnitude of instantaneous spatial vectors throughout the cardiac cycle. Such a curve can be transferred onto a flat sheet of paper, as maps are " projected " from the terrestrial globe onto a sheet (Steers, 1949). Thus one curve would supply the data (concerning spatial vector orientation) contained in the three loops of the cathode-ray vectorcardiogram. Such normal and abnormal curves are being studied at present at this laboratory as are tentatively called " single-curve vectorcardiograms."

Discussion

Using readily available recording apparatus the non-quantitative method of analysis described, yields certain characteristics of the spatial vector loop by simple inspection, as does the three-plane vectorcardiogram. This method may be applied to clinical problems as will be described in later studies.

Construction on the electrocardiographic strip or on two biaxial charts was used for quantitative determination of the magnitude and orientation of spatial vectors. A " blackboard globe " model was used only for the measurement of angles between vectors. Comparison with published descriptions of vector models shows the relative ease of using the globe. The latter is commercially available, thus no special apparatus need be built; instead of manipulating " vector rods " or pointers, two chalk marks are made; a large number of vectors can be simultaneously represented.

The coronal plane is " viewed " from above in most published work (Committee of American Heart Association, 1954); from below by Grant and Estes (1951), Shillingford and Brigden (1951), and with the present method. Reasons for choosing one of the two possible " points of view " are not given in most published studies. It was felt that with the present method, as scalar leads were used, " consistency in convention of sign " (Robertson, 1951) should be observed. Leads of the " cube " lead arrangement so recorded, resemble in their patterns conventional leads with parallel axes, facilitating correlation. Forward directed vectors give upward deflections in conventional leads with sagittal or near-sagittal axes (V1, 2, 3), also in " consistently " recorded lead Z. This is to say that these leads present the coronal plane as seen from below.

Summary

Methods for the determination of spatial cardiac vectors, from leads of the " cube " reference system, have been described. A two-channel scalar electrocardiograph was used to record a frontal lead-pair (caudo-cranial and transverse lead), and a coronal lead-pair (sagittal and transverse lead).

Spatial vectors and loops can be described in a non-quantitative fashion, from simple inspection of the two lead-pairs. A method for the quantitative determination of the magnitude and direction of spatial vectors, on the electrocardiographic strip or on two biaxial charts, is suggested. The longitude–latitude network of the terrestrial globe is used as a spatial coordinate system, to define the direction of spatial vectors. A terrestrial " blackboard globe " is used as a vector model, to determine the angle enclosed by two spatial vectors.

A new principle of representing all spatial vectors of a cardiac cycle by one symbol, the " single-curve vectorcardiogram," is discussed.

I wish to thank the Physicians to Green Lane Hospital for their permission to investigate patients in their care; the Medical Superintendent and the Board for their cooperation; and Drs. D. Brown and K. Kreielsheimer, Associate Professors of Physics, Auckland University College, for their advice concerning the mathematical aspects of this study.

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CORONARY DISEASE: A PATHOLOGICAL STUDY

BY

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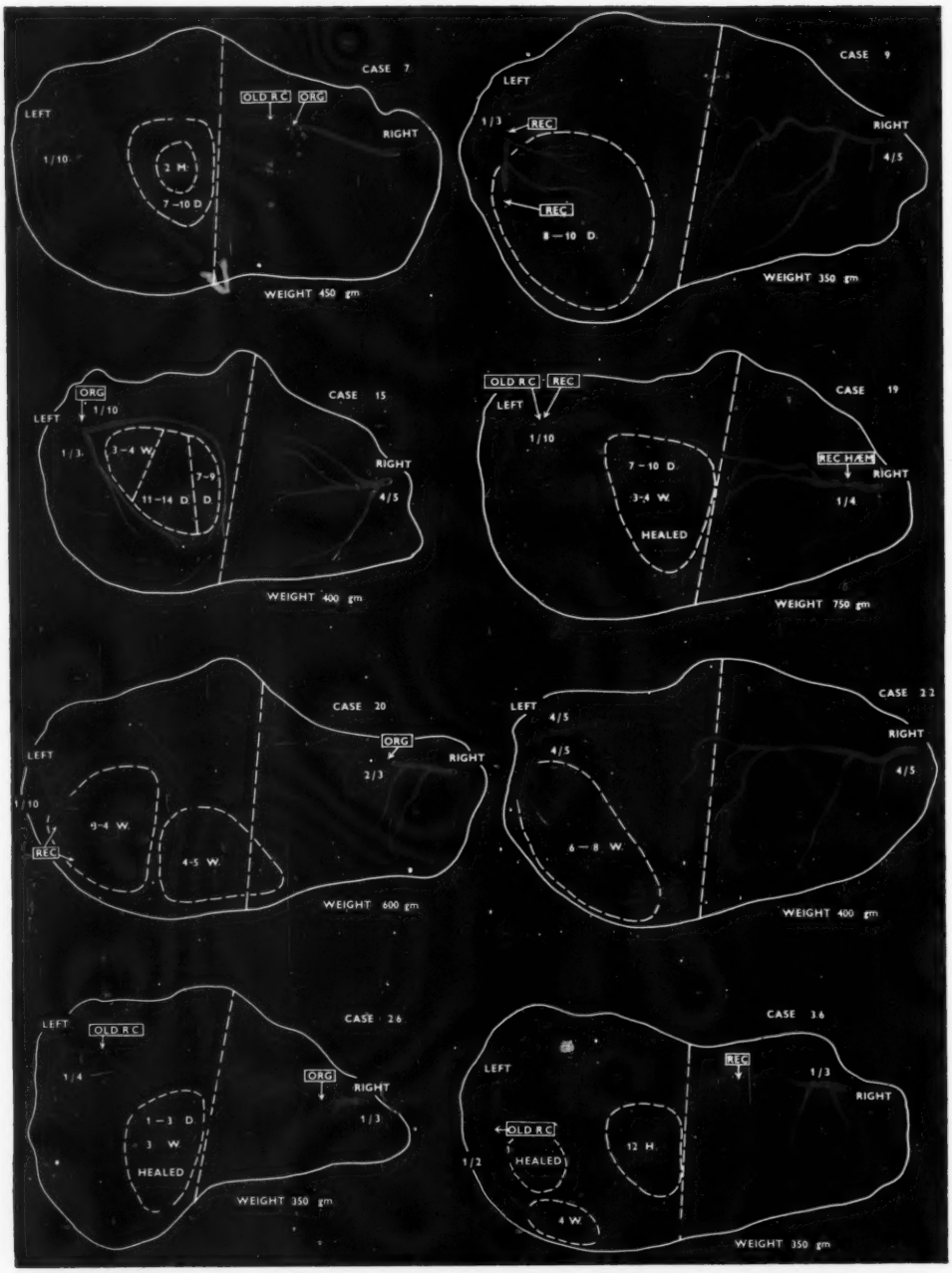
Since the diagnosis and management of coronary disease depend largely upon premises derived from pathological (and clinico-pathological) studies, the methods used in these types of investigation obviously require careful scrutiny. The focal point of such work is the detailed examination of the heart at necropsy, and the more accurate the methods used for this purpose, the greater the number of lesions revealed in the coronary arteries and myocardium. In previous work the introduction of new technical methods for studying either arterial or myocardial lesions has led to concentration upon the type of lesion that the new technique demonstrated, often to the comparative neglect of other lesions. Thus the detailed methods of examining the myocardium employed by Kossmann and de la Chappelle (1938), Lowe (1941) and Myers *et al.* (1947) were not combined with equally satisfactory methods of examining the coronary arteries, and the very careful study of the coronary arteries made by Blumgart *et al.* (1940) does not appear to have been combined with an equally comprehensive study of the myocardium. It therefore seemed worthwhile to reinvestigate the relationship between coronary artery occlusion and myocardial infarction by the best available techniques for the post-mortem study of both arterial and myocardial lesions.

METHODS

The method used to examine the coronary arteries was that devised by Schlesinger (1938). In addition, however, a detailed myocardial examination was made, with a comprehensive histological examination of all suspected arterial and myocardial lesions. Only an outline of the technique is given here for a detailed description will be published elsewhere. At autopsy the heart was removed entire and the coronary arteries cannulated under saline. The heart was then suspended in saline at 44° C. and the arteries perfused with normal saline till the washings returned clear. The radiopaque injection medium introduced by Schlesinger was then injected at a pressure of 140 mm. Hg. The heart was cooled in iced saline and unrolled so as to lie in one plane. A radiograph of the specimen was obtained by means of which all occlusions and points of narrowing can be recognized. Using the radiograph as a guide, the arteries were sectioned at 3–4 mm. intervals to confirm and extend the radiographic findings by naked eye and microscopic examination. Since the injection medium was red in the right coronary artery and blue in the left, the colour of the medium distal to an occlusion indicated the source of collateral channels. Serial sections were then taken through the whole heart at intervals of 0·5 cm. The myocardium was scrutinized and all suspicious portions removed for microscopic examination. If no naked eye abnormality was found, sections were routinely taken from the anterior, lateral, and posterior walls of the left ventricle and the posterior wall of the right, these being the sites at which infarcts are most likely to occur.

In assessing the number of infarcts, confluent or superimposed areas of infarction were regarded as separate incidents if the age of each portion was demonstrably different from that of contiguous areas. In practice this differentiation presents little difficulty. It is, however, necessary to emphasize that there are few areas of infarction in which the whole mass of muscle is necrosed: indeed if this did occur ventricular aneurysm or rupture would be the usual sequel of myocardial infarction.


CASE 7
LEFT
OLD R.C.
ORG
RIGHT
1/10
2 M.
7–10 D.
WEIGHT 450 gm
CASE 9
LEFT
1/3
REC
REC
8–10 D.
RIGHT
4/5
WEIGHT 350 gm
CASE 15
ORG
LEFT
1/10
1/3
3–4 W.
7–9 D.
11–14 D.
RIGHT
4/5
WEIGHT 400 gm
CASE 19
OLD R.C.
REC
LEFT
1/10
7–10 D.
3–4 W.
HEALED
REC HÆM
RIGHT
1/4
WEIGHT 750 gm
CASE 20
ORG
LEFT
RIGHT
2/3
1/10
REC
3–4 W.
4–5 W.
WEIGHT 600 gm
CASE 22
LEFT
4/5
4/5
RIGHT
4/5
6–8 W.
WEIGHT 400 gm
CASE 26
LEFT
OLD R.C.
1/4
ORG
RIGHT
1/3
1–3 D.
3 W.
HEALED
WEIGHT 350 gm
CASE 36
LEFT
REC
1/3
RIGHT
OLD R.C.
1/2
HEALED
12 H.
4 W.
WEIGHT 350 gm

In fact, throughout an infarcted area there remains a network of surviving muscle, which forms a living framework holding the islands of necrotic tissue together. These appearances are, of course, to be distinguished from the histological differences between the periphery and the centre of the same infarct due to more rapid healing at the periphery. Superimposition of successive incidents of infarction may therefore occur in the same area of myocardium. This concept is essential not only for the understanding of the pathology of infarction but also to appreciate the electrocardiographic features associated with extension of an infarct.

The possibility that some healed infarcts may have been due to aggregation of small areas of ischæmic fibrosis was considered, but in this series the same reticular pattern was found in old as in recent lesions, relatively large areas of fibrous replacement alternating with viable muscle. In ischæmic fibrosis, on the other hand, the replacement of muscle takes place fibre by fibre, and the more homogeneous appearance is readily distinguishable from that of infarction.

The ages of infarcts were assessed according to the criteria of Mallory *et al.* (1935). In our cases comparison of this assessment with the actual date of infarction, when this was clinically established, indicates that this method permits ageing within a day or two during the first week, within 4 or 5 days up to 3 weeks, and within 2–3 weeks up to 3 months. Unfortunately it was found impossible to assess the age of occlusions with a corresponding degree of accuracy for there seems to be considerable variation in the rate of organization.

Revascularized atheromatous plaques are to be distinguished from recanalized occlusions, which show the following features.

(1) Injection medium in the revascularized channels is in direct continuity with the medium in the artery proximal and distal to the arterial narrowing. This can be confirmed both histologically and radiographically.

(2) If more than one revascularized channel is present, all channels run parallel to the main arterial lumen.

(3) Cellular connective tissue is present in the wall of the revascularized channel.

For ease of assessment, all the pathological data were recorded in diagrammatic form on tracings of the injected heart (Fig. 1).

FIG. 1

Key: REC, recent occlusion; ORG, organizing occlusion; OLD R.C., old recanalized occlusion; D, days; W, weeks; M, months; H, hours; REC. HAEM., recent intimal hæmorrhage. The broken line divides the right and left ventricles.

Case 7.—An example of a recanalized occlusion transmitting a functionally significant blood supply. A more recent occlusion just proximal to it has caused a further infarct.

Case 9.—An example of occlusion without infarction. The more recent distal occlusion in the anterior descending branch of the left coronary artery has occurred within an already infarcted area.

Case 15.—An example of three confluent infarcts of different ages resulting from one occlusion. The presence of an extensive collateral circulation did not prevent extension of infarction. Note that the circumflex and anterior descending arteries arise by separate orifices.

Case 19.—An example in which there is some difficulty in interpretation. An old occlusion of the left circumflex branch led to a healed posterior infarct. This occlusion recanalized and subsequently reoccluded. The two more recent infarcts were probably due to the recent re-occlusion of the left circumflex branch and the hæmorrhagic narrowing of the right coronary respectively. It is possible, however, that both these infarcts could have arisen from either recent coronary obstruction. The left circumflex artery beyond the occlusion has been revascularized from the anterior descending branch.

Case 20.—A second example of an occlusion without a corresponding infarct. Both occlusions lie in the anterior descending branch of the left coronary artery within an infarcted area.

Case 22.—The only example in this series of an infarct occurring without any corresponding occlusion or significant narrowing of the coronary arteries.

Case 26.—The old recanalized occlusion of the circumflex branch of the left coronary artery is associated with a healed infarct at the apex of the left ventricle. A more recent occlusion of the right coronary artery has led to a 3-week-old infarct, which subsequently extended (1–3 days before death) into islands of surviving myocardium (superimposed extension).

Case 36.—An example of a single occlusion in the anterior descending branch of the left coronary artery causing two infarcts, separated by an area of uninfarcted myocardium. There is also a recent occlusion of the right coronary artery associated with a very recent infarct. It will be noted that there is some collateral vascularization from the left coronary artery. Collateral channels between the two coronary arteries may have been opened up following the old occlusion of the left coronary artery which subsequently recanalized.

Material

In order to make a comprehensive study of coronary disease, we have not confined our attention to cases with clinical manifestations, but have included cases of sudden death and patients in the appropriate age groups without clinical coronary disease who have died from other causes. The present paper is, however, limited to the first 25 cases of clinical coronary disease. Although the data presented here are purely pathological, it is intended to correlate them with the detailed clinical observations (which are also available in these cases) and this will form the subject of a separate paper.

Results

In 25 cases, 41 main vessel * occlusions and 59 infarcts were found.

Occlusions. Of the 41 occlusions, 17 were old and, rather surprisingly, all had recanalized; 14 showed no signs of organization and were classified as recent while 10 were of intermediate age and incompletely organized. In the anterior descending branch of the left coronary artery 23 occlusions occurred, 4 in the circumflex branch, and 14 in the right coronary artery.

Infarcts. Of the 59 infarcts, 18 were healed (3 months or more old) and 41 were sufficiently recent to permit histological estimation of their age. Two infarcts were found in the right ventricle in one heart, but all other infarcts were in the left ventricle or septum.

Occlusion without Infarction. In only 4 instances had occlusion of a main coronary artery failed to cause myocardial infarction. In each case the explanation was obvious, for the occlusion was the most recent of two or more in the same vessel, lay distal or immediately proximal to the earlier one and the area supplied by the vessel was already infarcted (Fig. 1, Cases 9 and 20).

Infarction without Occlusion. Only 4 areas of infarction were found without complete occlusions of the corresponding main coronary artery. In one case (Fig. 1, Case 22) a large infarct was present with only trivial narrowing of the arteries and without any clinical suggestion of major extra-coronary causes of generalized myocardial ischæmia. Another recent infarct (Fig. 1, Case 19) was associated with recent acute narrowing of a main coronary artery due to intimal hæmorrhage, and two other healed infarcts were associated with severe long-standing atheromatous narrowing of the corresponding arteries.

Multiple Infarcts due to a Single Occlusion. If we exclude these isolated incidents of infarction or occlusion, there remain 37 occlusions which had given rise to 55 infarcts. The additional 18 infarcts occurred in 13 cases in areas which could have been rendered ischæmic by existing occlusions. In 10 of these 13 cases a single occlusion had led to an infarct that subsequently extended on one or more occasions without further occlusion, so that there were contiguous or superimposed areas of infarction of demonstrably different ages (Fig. 1, Cases 15 and 26). In 2 of these 10 cases, the later infarct was adjacent to and confluent with the first, whereas in the other 8 cases the first and subsequent infarcts were superimposed, the islands of tissue surviving from the first infarct being affected by the later lesion. Either of these processes can reasonably be described as " extension " of an infarct, but we have been able to find little reference to them in previously published work on this subject. In the remaining 3 cases the infarcts were separated by an area of uninfarcted myocardium (Fig. 1, Case 36). In 9 cases the interval between the first and subsequent infarcts (due to a single occlusion) was known; in no case did this interval exceed eight weeks and in 7 cases it was less than three weeks. In our cases extension of infarction was not due to extension of the causative occlusion or to new occlusion, but to necrosis of already ischæmic muscle, a fact of some importance in considering the function of anticoagulant therapy.

It is notable that of the 18 instances of multiple infarction due to a single occlusion 16 were recent incidents. This is inevitable because the incidents of infarction are recognizable as separate events principally by the differing ages of the various areas, and when the infarcted area becomes fully healed this distinction is lost. It is impossible to say whether a completely healed area of infarction represents one or several incidents.

Revascularization of Infarcts. In radiographic injection studies of the coronary arteries areas of recent infarction may show up because there are few filled vessels in them (Fig. 2). As time passes the infarcted area becomes revascularized (Fig. 2) and is then indistinguishable on the radiograph though, of course, easily recognizable by naked eye and histological examination. Of the 59 infarcts in our series, 45 could be classified into " filled " or " unfilled " groups. These observations are correlated with the ages of the

* The term " main vessel " is used for the three principal coronary vessels—the right coronary artery and the anterior descending and circumflex branches of the left coronary artery.

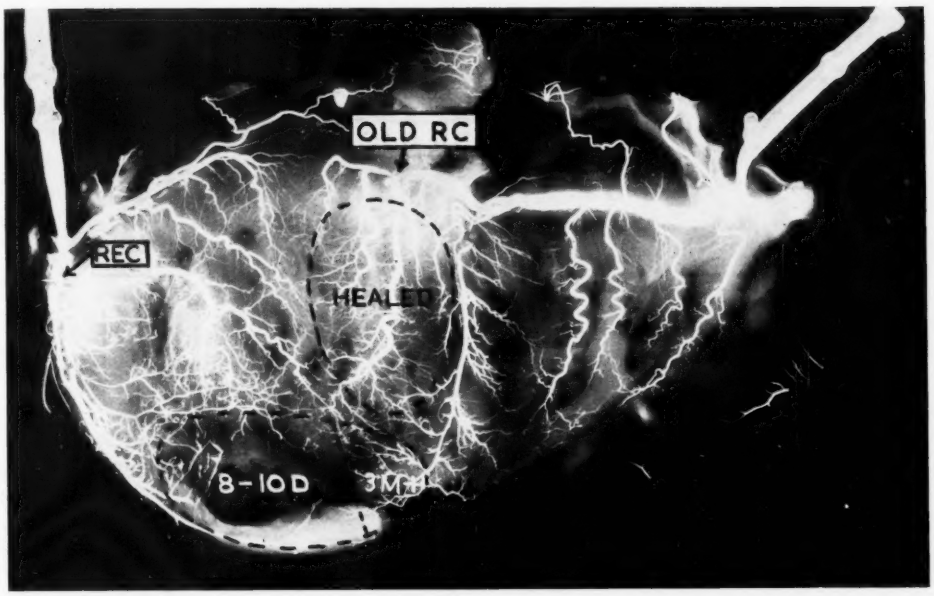


FIG. 2.—Radiograph of coronary arteries injected by Schlesinger's method. Three infarcts are present histologically. The healed and 3-months-old infarcts are well filled with injection mass, whereas the 8–10-day-old infarct is almost unfilled.

infarcts in Fig. 3. With the exception of three infarcts less than a week old, there is no evidence of arterial filling until the third week. Thereafter the proportion of infarcts that fill with injection medium increases until by the eighth week all infarcts are filled. It is concluded that revascularization of an infarcted area takes 3 to 8 weeks, the time probably depending upon the adequacy of the available collateral channels and the size of the infarct.

Three recent infarcts, aged 5–6 hours, 24–28 hours, and 5–6 days respectively, showed apparently normal filling (Fig. 3). Filling up to 24 hours may be explained by the fact that the arterioles in an infarct probably do not necrose as rapidly as the myocardium but this could scarcely explain the filling of an infarct 5–6 days old. The presence of injection medium in the infarct, distal to the occlusion, implies the presence of a collateral circulation which would aid survival of the vessels.

Collateral vascularization is not the only possible blood supply to an area of myocardium once supplied by a vessel that has become occluded. On the contrary, a fairly high proportion of old occlusions recanalize and this was true of all 17 old occlusions in our series. In 3 of these cases, further occlusions developed either in the recanalized channel or immediately adjacent to it, and in each case a further infarct resulted. A recanalized vessel can, therefore, provide a blood supply that is functionally significant.

DISCUSSION

In 1940 Blumgart, Schlesinger, and Davis undertook the first major study of coronary disease by the improved technique of coronary injection introduced by Schlesinger in 1938. In addition to their convincing demonstration of the frequency and extent of the collateral circulation in coronary disease, they put forward a new and important concept when they claimed that occlusion of a main coronary artery occurred very frequently in man without any corresponding myocardial infarction. This fitted in with their appraisal of the importance of the collateral circulation and has had a considerable influence upon the way in which both pathologists and clinicians have since thought about

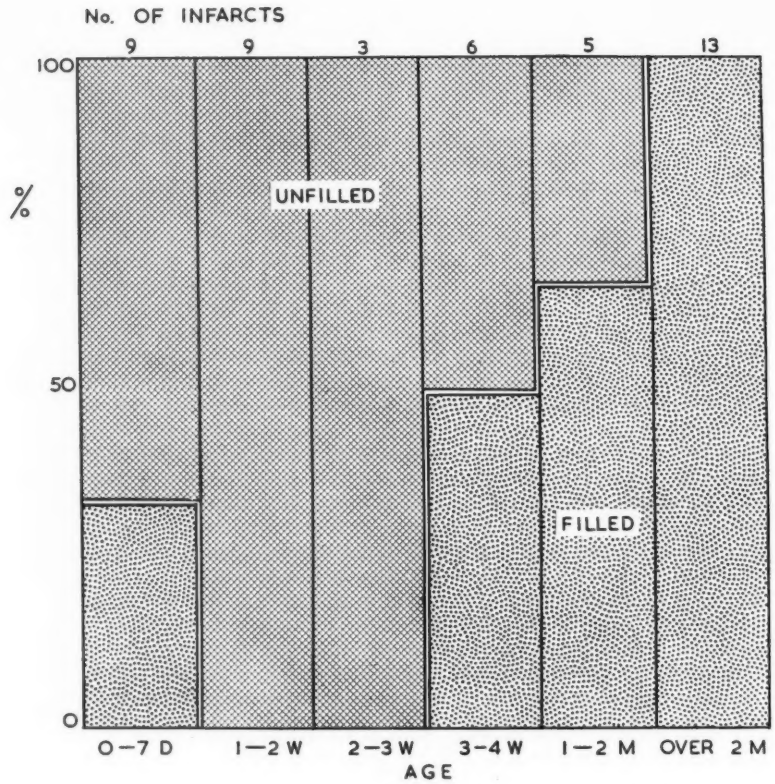


FIG. 3.—Diagram illustrating the time of filling of infarcts from collateral channels.

the sequence of events in the heart in coronary disease. It became easy for the pathologist to accept conspicuous coronary occlusion in the absence of demonstrated infarction, and when a prolonged attack of cardiac pain occurred without the associated changes of infarction in the electrocardiogram, the clinician was ready to attribute it to coronary occlusion without infarction. This concept naturally modified our clinical views upon the management of such cases.

When we began this study of coronary disease we expected to be able to confirm the views of Blumgart and his colleagues and anticipated that we would obtain figures for the incidence of infarction after occlusion similar to theirs in which, in 30 cases, 53 main vessel occlusions gave rise to only 16 myocardial infarcts. To our surprise, however, our own results have been strikingly different for in 25 cases, 37 of 41 main vessel occlusions led to at least one corresponding infarct in each instance. Further, in each of the four instances of occlusion without infarction, the occlusion was one of two in the same vessel, and the area supplied by that vessel was infarcted, so it is not surprising that the second occlusion failed to cause a second infarct. In conformity with traditional views, we are therefore obliged to conclude that when obstruction of a main coronary artery occurs in the human subject, it is almost inevitable that myocardial infarction will follow.

It seems important to discover the reasons for this major discrepancy between the results of two rather similar studies. Naturally we wondered whether there was any possibility that we had underestimated the frequency of occlusions in our cases, but on comparing our figures with those of

Blumgart and his colleagues we found that the incidence of occlusions was almost exactly the same in the two series (Table I). This table also shows that the discrepancy lies not in the frequency of occlusion, but in the frequency of infarction. Our technique for the recognition of myocardial

TABLE I

COMPARATIVE INCIDENCE OF CORONARY OCCLUSION AND FREQUENCY OF INFARCTION

	Blumgart, Schlesinger, and Davis (1940)	Present series
Cases	30	25
Major occlusions..	53 (1·8 per case)	41 (1·6 per case)
Infarcts. Total ..	16 (0·5 per case)	59 (2·4 per case)
Old ..	10	18
Recent ..	6	41

infarction consisted of a full search of the whole myocardium by the serial slice technique with histological examination of every suspected area, whether naked-eye changes were present or not. So far as we are able to ascertain from their published data no such examination was made in the cases of Blumgart and his colleagues. We are compelled to conclude that the discrepancy may be due, at least in part, to their failure to identify all infarcts, and we believe that this may have misled them in their estimate of the incidence of occlusion without infarction.

In considering the likelihood of occlusion without infarction in the human subject, it must be borne in mind that there is some evidence that major coronary occlusion can be induced in animals without causing infarction. Gregg *et al.* (1939) found that in the dog gradual occlusion of a main coronary artery in successive stages was often not accompanied by myocardial infarction, although sudden occlusion of a vessel of comparable size was followed by infarction. Gradual coronary occlusion cannot, of course, be recognized with certainty in human pathological studies, but in our cases there were 9 occlusions in vessels previously narrowed at that point by atheroma so that they appeared to be one-tenth or less of their original lumen. It seems reasonable to regard such occlusion as merely the final stage of a gradual narrowing, and in these circumstances there had been time for the development of a collateral circulation. None the less, in all these cases the final occlusion of the narrowed artery led to an infarct. So even comparatively gradual occlusion of a main coronary artery in man leads to infarction as a rule, and in this respect the human subject does not follow the pattern of animal experiments. The most obvious explanation for this difference is that in experimental animals the remaining unoccluded vessels are healthy whereas in the human subject they are often grossly narrowed, or already occluded, so that it is more difficult for an adequate collateral circulation to develop.

When we try to appraise the place of the collateral circulation in preserving the myocardium when coronary occlusion occurs, our results lead us to a conclusion rather different from that of Blumgart *et al.* (1940), for we find no evidence that the collateral circulation is capable of preventing infarction when a major coronary artery is occluded. Its function might lie in limiting the area of infarction, or in the prevention of subsequent extension of the infarct into adjacent ischæmic zones. We have therefore been interested in trying to study the frequency with which the area of infarction extends and in comparing the time during which extension may occur with the time necessary for the full development of the collateral circulation.

In 10 of our 25 cases a single occlusion resulted in an infarct that subsequently extended on one or more occasions without further occlusion. In 9 instances, the ages of the first and subsequent infarcts were accurately known and in no case did the interval between them exceed 8 weeks, and in 7 cases it was less than 3 weeks. The rate of revascularization of the peripheral ischæmic zone might be expected to determine the period during which extension of an infarct is liable to occur.

In our series the available evidence suggests that revascularization becomes complete between the third and the eighth weeks (Fig. 3).

Thus it seems that the liability for extension of an infarct passes away as the collateral circulation develops. Our views upon the function of the coronary collateral circulation in man are, therefore, that it probably cannot develop soon enough to prevent infarction when a major coronary artery is occluded, but that it may well serve to limit the area of infarction, and that its major function is the restoration of an adequate circulation to the surviving but ischæmic peripheral zone, so abolishing by degrees the tendency for extension of necrosis into adjacent ischæmic areas.

Summary

Twenty-five hearts from patients with clinical coronary disease have been subjected to detailed post-mortem examination, including coronary injection and comprehensive histological examination of the myocardium. The concept of the prevention of infarction by the development of collaterals concomitantly with gradual narrowing was not borne out. On the contrary, almost all occlusions (even in greatly narrowed arteries) gave rise to infarcts, and although collaterals developed they did not prevent infarction. Recanalized occlusions appear to be capable of transmitting a functionally significant blood supply for if they re-occlude new infarction follows.

Not only do major occlusions almost invariably cause infarction but in addition a single occlusion frequently gives rise to more than one infarct. In fact, extension of an infarct into adjacent ischæmic zones is a commonly observed pathological event, and this occurs without further coronary occlusion. This tendency for an infarct to extend exists for a period of 3 to 8 weeks after the original infarct, and this period corresponds closely with the time required for the full development of collateral vascularization of the ischæmic area. It is reasonable to conclude that the collateral circulation, when fully developed, plays an important part in preventing the extension of infarction by revascularizing adjacent ischæmic areas of myocardium.

We are indebted to Professor Crighton Bramwell for his interest in this work, to Professor A. C. P. Campbell for his advice on the pathological aspects and to Dr. D. A. K. Black for help in presentation of the results.

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PATENT DUCTUS ARTERIOSUS

SOME NOTES ON PROGNOSIS AND ON PULMONARY HYPERTENSION

BY

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Successful ligation of a patent ductus arteriosus was first reported by Gross and Hubbard in 1939. Since then an increasing number of physicians and surgeons have thought that all patients with this as the sole anomaly should be treated surgically. In this country Gilchrist (1945), in an excellent review of the subject, expressed the view that the ductus should be closed in children even with slight symptoms, and a similar view was expressed by Bourne (1945) and by East (1945). There are good reasons, because the studies of reported deaths by Bullock *et al.* (1939) and by Keys and Shapiro (1943) show that many patients die before 30 and still more before 40 years of age, although general experience and the follow-up studies of Wilson and Lubschez (1942) and of Benn (1947) show that the prognosis in children is excellent for many years.

The evidence for surgical closure of a ductus in every case is, however, not complete; for the natural prognosis is still uncertain and becomes more difficult to determine with the increasing proportion of children submitted to operation. The progress of older patients should help and so we have made an effort to re-examine all those over 35 years of age.

I. General Aspects

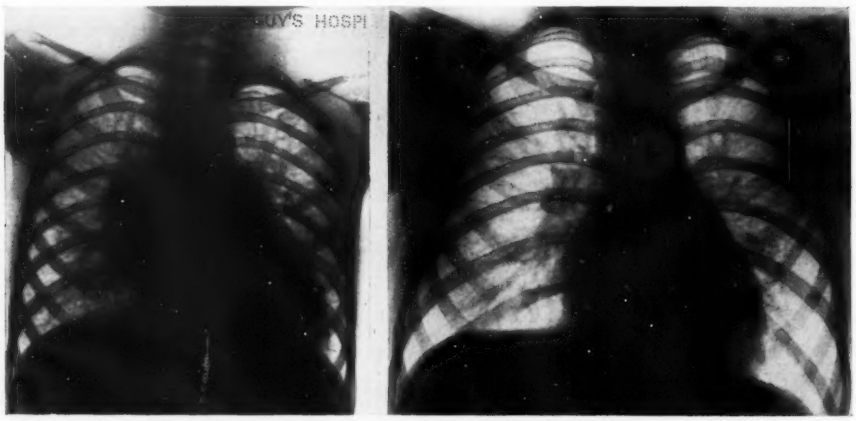
During the last few years we have seen 160 patients with a patent ductus, excluding 6 where there seemed to have been pulmonary hypertension from infancy with a balanced or reversed shunt (see p. 525) and excluding those with morbus cœruleus or with other abnormalities. The sex incidence shows the usual preponderance of girls with a proportion of 2·7:1, the excess showing equally at all ages and 27 per cent being male and 73 per cent female. The age incidence, when they were first seen, is shown in Table I: nearly half were under 10 years of age, probably because the diagnosis is often made at the first school examination, but a quarter were over 20 and twenty have been re-examined and followed generally for some years after they had passed 35 years of age.

TABLE I

Age and Sex Incidence of Patent Ductus Arteriosus

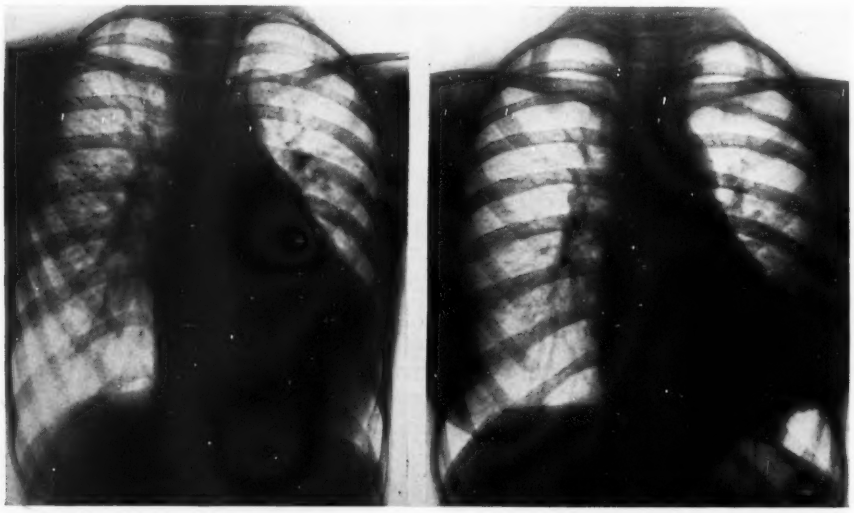
	Numbers at each age (in years)								
	0–4	5–9	10–14	15–19	20–24	25–29	30–34	35 and over	Total number
Male ..	7	11	5	9	4	2	2	3	43
Female ..	22	38	18	12	7	5	4	11	117
Percentage	18	30	14	13	8	4	4	9	160

We need not say much about the general features for Brown (1950) has given an excellent account. We would only comment shortly on the diagnosis and on his statement that a large heart is rare and suggests some additional abnormality. The heart is often large, sometimes very large with cardiothoracic ratios of 60 or 65 per cent, even in young children, and may return to a normal size after closure of the ductus (see Fig. 1 and 2) proving that this was the cause of the enlargement.



A B

FIG. 1.—A very large heart, becoming normal in size after closure of an uncomplicated patent ductus. (A) Before operation, c.t.r. 63 per cent (10·5/16·8 cm.). (B) Four years after operation, c.t.r. 49 per cent (11·2/23·0 cm.). From a girl, aged 5. Case P226.



A B

FIG. 2.—A very large heart becoming much smaller after closure of a patent ductus. (A) Before operation, c.t.r. 63 per cent (12·1/19·3 cm.). (B) Two years after operation, c.t.r. 54 per cent (11·6/21·4 cm.). From a girl, aged 12. Case O621.

We agree, of course, that often there is nothing more than some prominence of the left ventricle on radioscopy.

Diagnosis. This can be made on the continuous murmur in 95 per cent of cases. Cardiac catheterization should be used whenever there is any suggestion of right ventricular hypertrophy, to decide if this is due to pulmonary hypertension alone or to other complications, and whenever a patent ductus seems possible although the murmur is not a typical continuous one: this may apply to older patients where the murmur is disappearing or to young children before it has developed or where it is atypical. Aitken (1953) thinks this is common where there is a short wide ductus and that such children are liable to develop pulmonary hypertension. The only two young patients who have died had only systolic or atypical murmurs when they were first seen, and were waiting catheterization when they died elsewhere, one with bacterial endocarditis and one with hæmoptysis. These children emphasize the need for catheterization whenever a patent ductus seems a possible, even if unlikely, diagnosis. The continuous murmur is, however, generally reliable and few patients with long sytolic and diastolic murmurs that were not truly continuous have proved to have a patent ductus. Phonocardiography may be useful if there is doubt (Haring *et al.*, 1954).

Catheterization is generally decisive but it may fail. It failed in two patients where the diagnosis was proved by operation, presumably because the catheter had not passed far enough into the pulmonary artery. The second possible cause of failure is when the oxygen saturation increases in the right ventricle as well as in the pulmonary artery. This may be due to the addition of pulmonary regurgitation or to a shunt through a ventricular septal defect, and can provide a difficult diagnostic problem, as in our Case 24. Cournand *et al.* (1949) described one patient where a patent ductus with pulmonary regurgitation wrongly suggested that there was a ventricular septal defect and another where necropsy confirmed that both lesions were present.

Spontaneous Closure of the Ductus. A machinery murmur may regress and disappear. This happened five times in the series of Brown and Muir, once at the age of 34 after 17 years observation (Brown, 1950), and Benn (1947) reported two examples at the ages of 25 and 27 after the murmur had been observed since childhood. Our Cases 1 and 2 have nearly reached this stage and so has a young man, aged 20, who had been successful in cross-country running in the army; the murmur was getting fainter and catheterization showed a rise of O_2 percentage saturation that was not decisive, from 80 in the RA and 76 in the RV to 78 in the right and 84 per cent in the left pulmonary artery. Nevertheless, this does not happen often enough to be any reason for deferring operation, unless the patient shows signs that the ductus is already closing.

Operative Treatment and Mortality. Many of the older patients lose ground (see later) and this supports the view that all those with a patent ductus should have an operation when the diagnosis is made. Of the 160 patients, 20 who have passed the age of 35 years will be discussed fully in the next section. This leaves 140 patients under 35 years of age. Two died before the diagnosis was established and 111 have had operation for closing the ductus. There are another 10 who have been advised to have an operation and 12 who are to be seen again for a final decision. This means that there are only 5 where operation has not been advised because the shunt is thought to be so small that the ductus seems more likely to close than to cause difficulties. In two of these, though I have little doubt of the diagnosis, catheterization has failed to prove it.

Operation has been carried out in 119 patients. I have been fortunate in the surgeons available and among the ordinary patients, including eight over 35 and another fourteen over 20 years of age and several with pulmonary hypertension there has been only one death. There were, however, four deaths in more complicated cases—two where the shunt had become reversed (Case 19) or balanced (Case 28) and two where unsuccessful operations had been performed elsewhere; in one of these the ductus had recanalized (Case 23) and in the other the pulmonary artery had been ligated in error (Milstein and Brock, 1954, Case 15).

This also happened in Case 4 of Bonham-Carter *et al.* (1955) and nearly we think in another patient, aged 22, where nothing was done because occlusion of " the ductus " was said to be without effect on the thrill. When he was seen, clinical examination and catheterization suggested

a ductus, and when this was closed by Mr. Tubbs, who found nothing out of the ordinary, his murmur disappeared, his heart became smaller, and he lost all his symptoms. Such examples are mentioned lest the success and low mortality of experienced surgeons should suggest that there is little risk. A very low mortality at operation is essential if it is to be advised in all patients, even when they are free from symptoms.

The patient who died was 16, and the vessels were not easy to deal with in one girl of 17 and in two girls of 19 and 20 years. Difficulties are rarely encountered in patients under 15, but once the diagnosis has been made there is no object in deferring operation. This series does, however, show that where the opportunity has been missed at an earlier age, there is no undue risk in older patients though auricular fibrillation may occur for a time after operation.

Results of Operations. These have been excellent and we have little to add as our experience is the same as that of others in the series that have been reported. So far as we know there are only two patients who have caused anxiety afterwards: one had a cerebral abscess without evidence of bacterial endocarditis two years later and the other is the only one where the ductus has partly recanalized. She was a girl, aged 19, with some aneurysmal dilatation of the ductus and the aorta, and Mr. Holmes Sellors was asked to carry out the operation which, as expected, was difficult. Four years later she seemed well but a fainter continuous murmur was heard again; the flow through the ductus can not have been very large for the heart was smaller than before (c.t.r. 57 instead of 64%) but not normal. Probably this difficulty would not have arisen had the ductus been closed some years earlier: such problems are inevitable at present but should arise less often in the future.

In most cases the heart becomes normal in size or nearly so. Sometimes this happens quickly after operation but sometimes more slowly, only becoming normal as the chest grows with the child's growth, e.g. in one girl the cardiothoracic ratio fell gradually from 63 to 54 per cent in the course of three years (Fig. 2).

Although in general the operation is done to help the patients in the future rather than at once, some find they were more disabled than they thought and others find the reduction in the large pulmonary blood flow makes their liability to bronchial attacks and pulmonary congestion much less. One girl had severe asthma with frequent attacks of bronchitis and congestion, and her mother was warned that much improvement in this direction could not be promised: in fact, four years after, her asthmatic attacks are almost cured, being trivial affairs of a day or so instead of a constant cause of anxiety through the winter, and her heart is much smaller (Fig. 1).

Cardiologists are rightly reluctant to admit fatigue as an important cardiac symptom, but it must be accepted as typical of some patients with a large ductus although many have unlimited energy: such fatigue may disappear completely after a successful operation. This is in line with the suggestion of Gorlin (1954) that fatigue is common with severe mitral incompetence because of the small systemic flow.

II. The Progress of Older Patients

We have seen 20 patients over 35 years of age who still had or were known to have had a typical continuous murmur (see Table II). The main results obtained in those who had cardiac catheterization are given in Table IV, where the size of the shunt is expressed as a percentage of the pulmonary flow which is, of course, in the case of a patent ductus the same as the left ventricular output. For convenience in comparing results expressed as ratios of the pulmonary and systemic flows, the relationship of these two methods is shown in Table III, and this is applicable to all forms of left-to-right shunt.

We have divided these patients into five groups (1) those with the ductus almost closed, (2) those still doing well, (3) those apparently well but with a large heart or right ventricular strain, (4) those losing ground, and (5) those who have died. All had got on well in early life; 11 of the 15 women married and all but two of these had borne children without any special difficulty.

TABLE II

OLDER PATIENTS WITH PATENT DUCTUS ARTERIOSUS

Case No.	Sex and age	Heart size c.t.r. (%)	Blood pressure and pulse pressure	Shunt as percentage of LV output (%)	PA pressure	Electrocardiogram
1 (H273)	M37–44	48	120/75 45	—	—	No LVP
2 (1230)	F31–38	42	145/85 60	—	—	No LVP
3 (1155)	F44	51	160/90 70	?	20/10	LVP
4 (1202)	F38	42	145/85 60	—	—	Slight LVP
5 (CB30)	F60–62	60	130/65 65	48	23/10	LVS. T inv. in I, V5, V6 (Fig. 3)
6 (O326)	F41–47	57	180/80 100	—	—	LVP only
7 (O612)	M36–40	56	125/65 60	—	—	LVP only
8 (H305)	F43–48	55	145/65 80	57	13/5	LVP only
9 (P214)	M34–40	53	130/70 60	—	—	LVS. T inv. in I
10 (1213)	F29–35*	68	130/50 80	57	45/35	LVS. T inv. in V4, V5, V6 (Fig. 4)
11 (1110)	F45*	68	130/50 80	72	68/40	LVS. T inv. in I, VL, V6
12 (P318)	M42	63	125/65 60	—	—	LVS. T inv. in I, V6
13 (H328)	F41*	50	170/60 110	62	22/11	LVP. T flat in L, VI, V6
14 (H303)	F35*	68	180/20 160	64	39 mean	LVS
15 (O582)	M34–38*	54	130/70 60	58	45/25	LVP → LVS (Fig. 6)
16 (P342)	F53*	65	145/65 80	50	26/16	LVS
17 (O532)	F28–35*	69	140/70 70	65	36/16	RVP from pulmonary stenonis
18 (H287)	F39	73	140/60 80	—	—	Balanced; T small in I and V6
19 (P177)	F40†	60	125/65 60	—	110/65	LVS. T inv. in I, VL, V4–V6. Some RVH
20 (H306)	F32–38	64	180/20 160	—	—	1948 LVP; 1954 LVS. T inv. in I, VL, V5, V6
21 (O280)	M27*	48	130/50 80	32	18	LVP only
22 (P316)	M26*	56	140/60 80	68	78/54	Bilateral vent. hypertrophy (BVH)
23 (P314)	F26†	59	160/60 100	70	65/39	BVH and flat or inv. T waves
24 (O891)	F30–34)	66	155/59 96	50	20/5	1952, LVP; 1955, early LVS, small T in I and V6

* Have had operations. † Died after operations.

TABLE III

THE SIZE OF LEFT-TO-RIGHT SHUNTS RELATED TO SYSTEMIC AND PULMONARY FLOWS

Size of shunt (litre/min.)	Shunt as percentage of pulmonary flow (%)	Pulmonary flow (litres/min.)	Systemic flow (litres/min.)	Pulmonary flow/systemic flow
2	33	6	4	1·5
4	50	8	4	2·0
6	60	10	4	2·5
8	66	12	4	3·0
12	75	16	4	4·0
16	80	20	4	5·0

This table is equally applicable to all uncomplicated left-to-right shunts—atrial and ventricular septal defects as well as patent ductus. It has been calculated on the assumption that the systemic flow remains constant at 4 litres a minute.

TABLE IV

SOME FINDINGS AT CARDIAC CATHETERIZATION IN PATIENTS WITH PATENT DUCTUS ARTERIOSUS

Case No.	Sex and age	O_2 percentage				Pressures (mm. Hg)			Flows* Litres/min.		Shunt as percentage of LV output (%)
		RA	RV	PA	Syst. art.	RV	PA	Syst. art.	Syst.	Pulm.	
3	F44	(86)	73	84	99	19/4	19/9	160/90	—	—	—
5	F60	65	62	75	97	24/2	23/10	130/65	3·5(2·3)	6·7(4·5)	48
8	F48	71	66	86	92	18/2	13/5	145/65	5·3(3·7)	12·5(8·8)	57
10	F35	68	71	86	99	55/5	45/35	130/50	5·9(3·6)	13·8(8·6)	57
11	F45	53	56	86	96	65/4	68/40	130/50	3·7(2·3)	13·2(8·4)	72
13	F41	53	52	75	(90)	23/0	22/11	170/60	4·5(3·2)	11·6(8·3)	62
14	F35	62	66	88	94	20	39	180/20	4·0? —	12·0? —	65
15	M38	68	65	86	99	45/6	45/25	130/70	4·3(2·5)	10·3(6·0)	58
16	F53	60	64	75	95	26/5	26/16	140/65	5·1(3·2)	10·0(6·2)	48
17†	F35	60	59	86	97	158/10†	36/16	140/70	3·3(2·0)	10·0(6·0)	65
19	F40	—	—	—	—	—	110/65	125/65	—	—	—
21	M27	66	72	80	95	14	18	130/50	5·2(3·1)	7·6(4·4)	32
22	M26	59	63	83	92	77/3	78/54	140/60	5·9(3·4)	18·5(10·8)	68
23	F26	57	60	86	97	62/6	65/39	100/50	3·8(2·3)	13·5(8·2)	71
24	F30	63	80	81	96	24/2	20/5	140/60	5·4(3·6)	10·9(7·2)	50

* The figures in brackets give the cardiac index (litres/sq.m./minute).
† This patient had pulmonary valve stenosis as well.

Older Patients with the Ductus almost Closed

The two patients in this group were leading normal lives without symptoms. The continuous murmur was very faint and localized under the left clavicle and could easily be missed. Neither had any enlargement of the heart or ventricular preponderance in the electrocardiogram; Case 1 was the only one of the 20 older patients with a pulse pressure under 60 mm. Neither has had catheterization but the shunt through the ductus must be small.

Case 1. A man, aged 37–44,* was leading a normal life. His continuous murmur had been missed at a previous examination for life insurance and when he had an operation, although it had been obvious when he was a boy. His earlier notes were available at the Heart Hospital and 30 years before Dr. Parsons-Smith had recorded a typical continuous murmur.

Case 2. A woman, aged 31–38, had no symptoms and was seen only because she brought up her daughter with coarctation of the aorta. Almost certainly the murmur had been much louder for a ductus had been diagnosed confidently when she was at school.

Older Patients still Doing Well

The three patients in this group were all leading normal lives, and only the woman of 60 complained of any symptoms or had any cardiac enlargement or left ventricular strain; she can only be included here because she had been so well till she was 50. All had continuous murmurs and pulse pressures between 60 and 70. The two who had catheterization did not show any rise of pulmonary arterial pressure (23/10 and 26/10 mm. Hg).

Case 3. A woman, aged 44, married and with three children, was seen only because her dentist wanted an opinion about her heart. She had no cardiac symptoms and though there seemed no doubt about the diagnosis, catheterization was indecisive (see Table IV).

Case 4. A woman, aged 38, was leading a normal life without symptoms and had two children, though she had been given a bad prognosis when a child. Catheterization was refused but it seems unlikely that operation is indicated here.

Case 5. A woman, aged 60–62, had noticed some dyspnœa for ten years and had a large heart (c.t.r. 60%) and left ventricular strain (see Fig. 3). Catheterization showed that half the left ventricular output was flowing through the ductus.

* Where two ages are given this indicates the time he has been under my observation before operation.

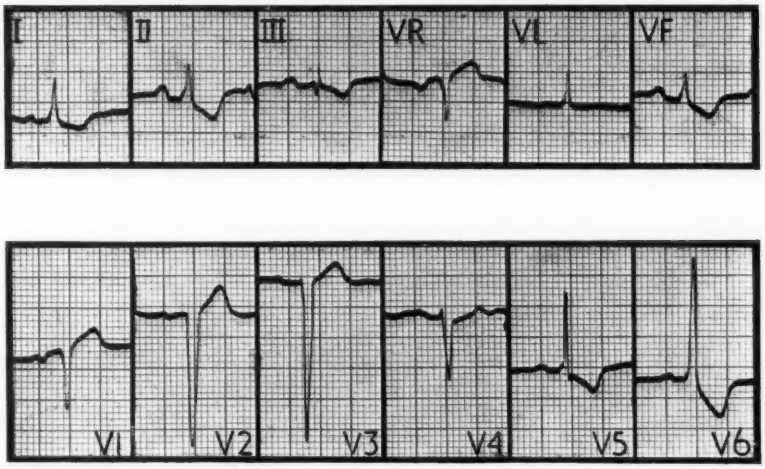


FIG. 3.—Left ventricular preponderance and strain with T inversion in the standard leads and in VF, V5, and V6, from a woman, aged 62, who had hardly been breathless till the last ten years. Standardization is normal, 1 Mv.=1 cm., in this and other figures unless stated otherwise. Case 5.

Older Patients Apparently well but with Large Hearts or Left Ventricular Strain

All the six patients in this group had typical continuous murmurs, except Case 11, who was losing it and generally had only a systolic murmur. All had rather wide pulse pressures from 60 to 100 mm. and all had large hearts, the cardiothoracic ratio being over 65 per cent in two. All had left ventricular preponderance and 3 of the 6 had left ventricular strain (Fig. 4). Between 57 and 70 per cent of the left ventricular output was passing through the ductus in the three who had catheterization and the pulmonary arterial pressure was 13/5 in Case 8, 45/35 in Case 10, and 68/40 mm. Hg in Case 11.

Case 6. A woman, aged 41–47, was admitted with bacterial endocarditis, having been almost symptomless up to that time. After she had made a good recovery she was advised to have an operation but refused. She has remained well for 6 years since this and her heart has not become larger (c.t.r. 57%).

Case 7. A man, aged 36–40, had hardly any symptoms and was working as a cook. Operation was not advised and four years later there has been no increase in symptoms, heart size (c.t.r. 56%), or left ventricular preponderance.

Case 8. A woman, aged 43–48, had been well all her life and at regular work, but was getting more disabled. Operation was refused and she has improved symptomatically during the next five years and resumed work, but the heart is getting larger (c.t.r. 58 instead of 55%). She has now had catheterization but operation has not been advised in view of her improvement.

Case 9. A man, aged 34–40, was seen because he was anxious to continue flying: he was leading a normal life with only slight dyspnœa but there was some left ventricular strain. Operation was not advised though in retrospect I think this was wrong. He is now in Africa and writes that he is well and has noticed no change in his capacity.

Case 10. A woman, aged 29–35, complained of some dyspnœa but was able to lead a normal life, though her heart was large. Six years later, she was more breathless, the heart was larger (c.t.r. 65 to 68%) and there was severe left ventricular strain (Fig. 4). The pulmonary arterial pressure was only slightly raised, 45/35. Operation was advised and during the six months she was waiting she became worse and was glad that she had accepted it. Three months after, she is much better, the pulse pressure is 40 instead of 80, and the heart is already smaller (c.t.r. 60 instead of 68%).

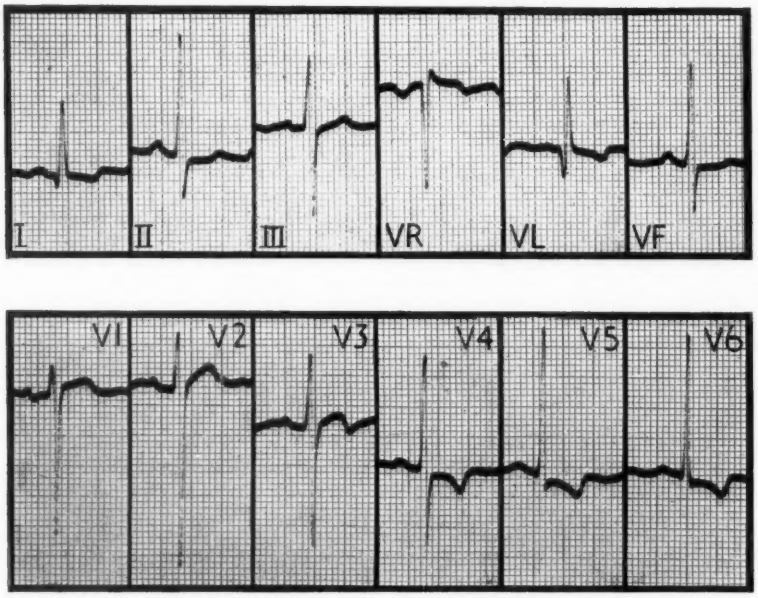


FIG. 4.—Left ventricular preponderance and strain from a woman, aged 35, with a patent ductus and a large heart. The T waves are biphasic in leads I and V3, and inverted in VL, V4, V5, and V6. The patient has since had a successful operation and there is less LV strain. Case 10.

Case 11. A woman, aged 45, did not notice much dyspnœa though she had a very large heart: generally only a systolic murmur was heard but occasionally a continuous murmur. The pulmonary pressure was 68/40 when the aortic pressure was 130/50 which probably explains why there was generally no murmur during diastole. The ductus was divided by Mr. Brain and the pulmonary arterial pressure fell at once from 57/47 to 39/27 mm. Three months later she was more active; the pulse pressure was smaller, the left ventricular strain was less, and her heart was already smaller (c.t.r. 63 instead of 68%).

Older Patients Losing Ground

All the 6 patients in this group had classical continuous murmurs and pulse pressures from 60 to over 100 mm. All except Cases 16 and 17 had left ventricular strain (Fig. 6), sometimes severe. All except Case 13 had large hearts, the cardiothoracic ratio being over 60 per cent in four. All were finding it difficult to carry on their normal activity or were more seriously disabled. Catheterization was performed in five of them and showed that they all had large shunts, but no larger than in most of the other patients, 50 to 65 per cent of the left ventricular output passing through the ductus. The pulmonary arterial pressure was normal in 2 and slightly raised in 3 (see Table IV).

Case 12. An Indian, aged 42, had been increasingly disabled since he was 37 with paroxysmal tachycardia and early left ventricular failure. His heart was large and there was left ventricular strain. He came to this country for catheterization and operation but refused both.

Case 13. A woman, aged 41, had been very well but was finding her daily work difficult. The pulse pressure was wide, 170/60, and it is surprising that there was no enlargement of her heart (Fig. 5). A year later, she could not manage her work so operation was carried out by Mr. Holmes Sellors. Four years later her condition is excellent and there is less left ventricular strain.

Case 14. A woman, aged 35, developed auricular fibrillation and was hardly able to do anything from the age of 32 years. The heart was large (c.t.r. 68%) and the pulse pressure very wide for a patent ductus, about 180/20; the pulmonary arterial mean pressure was 39 mm. She is much better after operation and has lost some of her left ventricular strain.

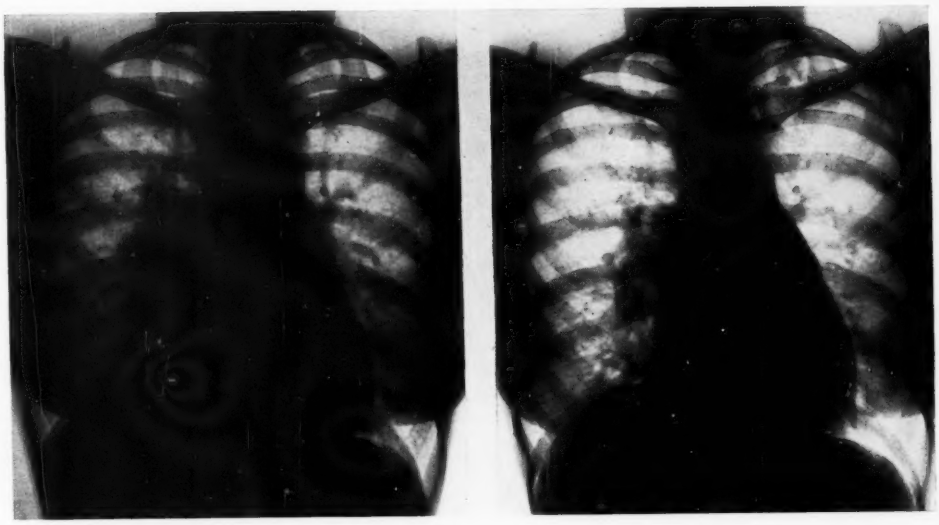


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FIG. 5.—A heart that was normal in size (c.t.r. 50%: 11·0/22·0 cm.) although the patient was 42 years old and had a large shunt through a patent ductus. (A) Before operation, with very pleonæmic lungs. (B) After closure of the ductus, showing less pleonæmic lungs. Case 13.

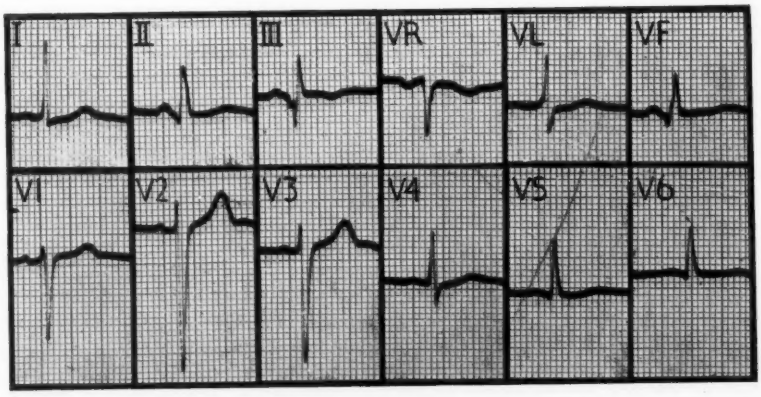

FIG. 6.—Left ventricular preponderance with early signs of strain: the T waves are small or flat in V4, V5, and V6, though they had been upright four years before. From a man, aged 38, with a patent ductus and a large heart, who has since had a successful operation. Three months later, the T waves were again upright in leads V5 and V6. Standardization in chest leads, half normal, 1 Mv.=0·5 cm. Case 15.

Case 15. A man, aged 34–38, had been fairly well when he was first seen but four years later was finding his work difficult. The heart was large and the T waves were now flat in V4–V6 (Fig. 6) though they had been upright before: the pulmonary arterial pressure was raised, 45/25 mm. His ductus has been closed and after three months he feels much better, the pulse pressure is normal, the heart smaller (c.t.r. 50 instead of 54%), and the T waves in V4–V6 are again upright.

Case 16. A woman, aged 53, was not allowed to do much as a girl because of her heart but led a normal life afterwards. When she was 48 she became breathless playing golf and was advised to have an operation for her patent ductus. She did nothing about this for five years, by which time she had developed cardiac asthma and slight congestive failure. The heart was very large (c.t.r. 65%) and there was left ventricular strain but no rise of pulmonary arterial pressure. A successful operation has been carried out recently.

Case 17. A woman, aged 28–36, had congenital pulmonary stenosis as well as a patent ductus. She had a typical continuous murmur and a large heart (c.t.r. 69%), but still led an active life. The high pressure in the right ventricle (158/10 mm.) and the preponderance of this ventricle suggested that it was no use closing the ductus without pulmonary valvotomy, and this seemed too dangerous while she was so well. When she was 36, however, her increasing disability and heart size were thought to justify the risk, and the ductus was closed and pulmonary valvotomy performed. A year later, she could again lead an active life and the heart was much smaller (c.t.r. from 69 to 55%).

Older Patients who have Died

The three patients who have died illustrate three different dangers: one died from heart failure with a balanced shunt; one died a few days after closure of the ductus nine months after the shunt had become reversed; and the third died suddenly. They provide further evidence that operation should be considered even in older patients whenever an experienced surgeon is available.

Case 18. A woman, aged 39, was admitted with congestive heart failure; she had a large heart and a systolic murmur only and was thought to have an atrial septal defect. After necropsy when the ductus was found patent we were able to trace the hospital where she had been nine years before with pneumonia and she then had a classical continuous murmur. She has been reported (Campbell and Hudson, 1952).

Case 19. A woman, aged 40, had a few symptoms and played tennis up to her marriage at 29 years. She was seen then by Dr. H. D. Heimann of Johannesburg, who found that she had a continuous murmur and a large heart (c.t.r. 57%). She had one child and was fairly well until she was 36, after which she became breathless and began to feel faint on exertion and lost consciousness unless she was careful to stop at once. When she was 39, any exertion brought on cyanosis that was confined to the lower limbs and the left arm.

At catheterization by Dr. R. H. Goetz in South Africa, the catheter passed through the ductus into the aorta; at rest the pulmonary pressure was sometimes 15 mm. lower than the aortic, but it was sometimes higher, as presumably it always was on exertion. There was a systolic murmur and thrill in the pulmonary area and below this a long loud diastolic murmur and thrill that were thought to be due to pulmonary regurgitation; this was confirmed by its persistance after the ductus was closed. Her heart (c.t.r. 60%) and the pulmonary arteries had become even larger (Fig. 7). The cardiogram showed mainly left ventricular strain but an R wave of 10 mm. in VI showed right ventricular hypertrophy also (Fig. 8). Her hæmoglobin was 120 per cent.

She was seen nine months after the first reversal of her shunt and was getting worse, so the ductus was closed by Sir Russell Brock. The aorta and pulmonary artery were both very large, and the ductus was calcified and 25 mm. in diameter at the aortic end. The pressures were very low during operation but closing the ductus with the finger increased the pulmonary arterial pressure to 70/48 against 37/29 in the aorta, compared with 37/35 and 45/35 respectively just before. Her condition was never good and auricular fibrillation started two days later and was difficult to control. The next day she died suddenly. There was no necropsy.

Case 20. A woman, aged 32–38, was somewhat breathless but led a normal quiet life with sedentary work. The extreme carotid pulsation and water hammer pulse with a blood pressure 200/20–50 suggested aortic incompetence and were much more than is usual with a ductus, but the murmur and its site were typical. She was advised to have an operation but refused.

Six years later, when she was 38, she wrote that she was getting on well though troubled by frequent paroxysms of tachycardia that were reduced in frequency by quinidine. Some weeks later she was admitted because of a longer paroxysm which was finally stopped with procaine amide. The physical signs and the wide pulse pressure were much the same and the heart was no larger (c.t.r. 64%) but there was more left ventricular strain. It was, in fact, surprising that she had done as well for so long. She again refused operation and was due to go home. One night she had a paroxysm at a rate of 160 for fourteen hours: she seemed as usual the next morning, ate her lunch without complaint, and started to get out of bed when she fell back dead. There had been some small spikes of temperature during the last ten days.

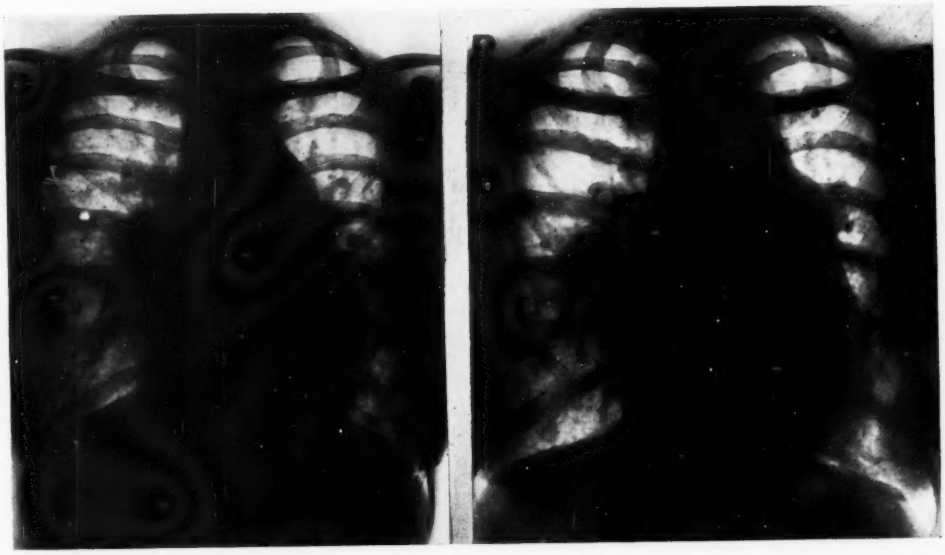

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FIG. 7.—(A) A large heart (c.t.r. 57%: 12·9/22·6 cm.) from a patient with a patent ductus and only moderate symptoms. (B) From the same patient ten years later showing a larger heart (c.t.r. 60%: 14·1/23·4 cm.) and still larger pulmonary arteries about nine months after the flow through her ductus had become reversed. Case 19.

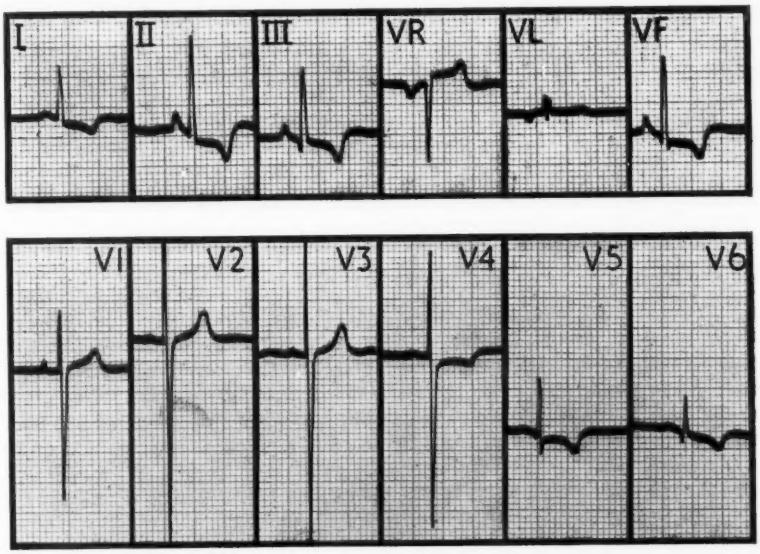

FIG. 8.—Biventricular hypertrophy in the electrocardiogram. There are relatively large R waves in V1. Although the pulmonary arterial pressure had risen high enough to reverse her shunt through the ductus for nine months, there is more evidence of strain on the left ventricle which had probably been progressive for 40 years while the strain on the right ventricle was more recent. Standardization, in chest leads, half normal, 1 Mv.=0·5 cm. Case 19.

Necropsy. The heart weighed 600 g. The right ventricle was hypertrophied to 7 mm. and the left to 17 mm. The pulmonary valve ring measured 77 mm., and the pulmonary trunk and main branches were thin-walled and dilated. The aortic vale ring measured 65 mm. and the cusps were thickened; just below there were the renants of a sub-aortic fibrous band but no stenosis (Fig. 9). The aorta showed minimal atheroma. The ductus was patent, and its aortic orifice was bowl-shaped and 15 mm. wide, while it was only 10 by 5 mm. at the pulmonary end. Just below the pulmonary orifice was a flat mural thrombus about 15 mm. by 5 mm.: this did not look infected but proved to be so, and thus infective endoarteritis was probably the cause of her more frequent paroxysms and indirectly of her death.

On histological examination there was congestion of the capillaries of the lungs and light cellular exudate in the alveoli. No emboli were found in the lungs and the vessels were within normal limits. There was, therefore, no confirmation of pulmonary hypertension though the hypertrophy of the right ventricle suggested that it might have started.

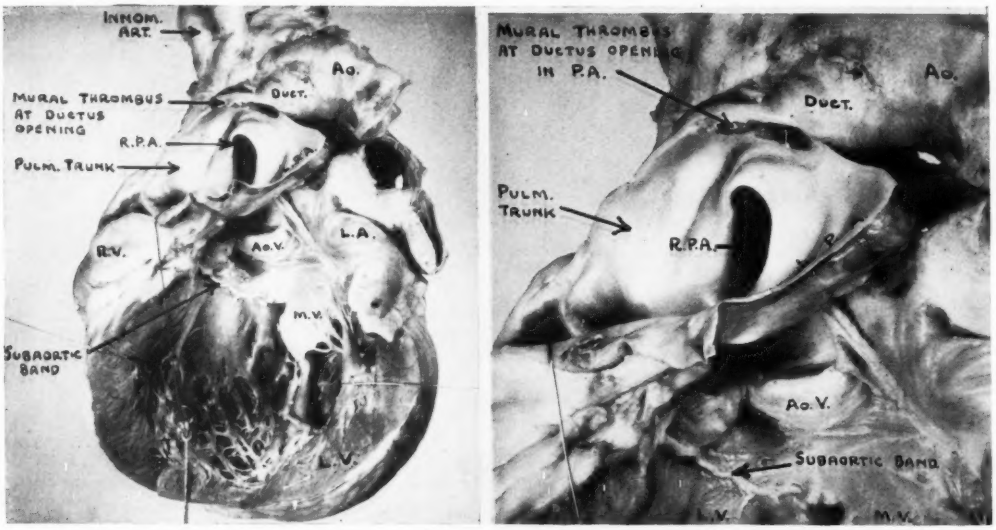

FIG. 9.—The heart opened to show the very large left ventricle. The large bowl-shaped patent ductus arteriosus is seen, and at its lower opening into the left pulmonary artery there is a rather flat mural thrombus. Below the aortic valve the remains of a sub-aortic fibrous band is clearly seen, but it was not causing any stenosis. Ao=Aorta, Ao. V=Aortic valve, and MV=Mitral valve. Case 20.

Some Younger Patients

Nine patients between 25 and 34 will be referred to shortly. Three of them were well and seemed likely to continue so, but are being seen again to reconsider surgical treatment. Two others, aged 25 and 30, had operations on general principles although they were not losing ground. In the former, the continuous murmur was quite typical, but had not developed when she was eight years old: I had made notes that no murmur could be heard in diastole in any position or after exercise and had not, therefore, made the correct diagnosis.

The other four provide some support for the view that a patent ductus should always be closed.

Case 21. A man, aged 27, had been in the army but afterwards found his work as a decorator getting more difficult. Operation was carried out successfully.

Case 22. A man, aged 26, had been losing ground for two years with frequent paroxysms of tachycardia: his heart was large and his pulmonary arterial pressure had risen to 78/54, so that the murmur might not have remained a continuous one much longer. There was some left ventricular strain and also some right ventricular hypertrophy, R in V3R being as large as S (Fig. 10). He has been well since operation.

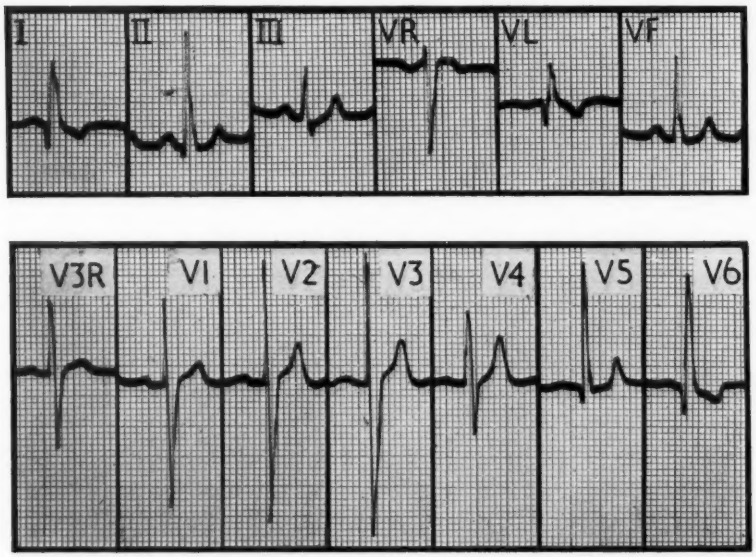

FIG. 10.—Biventricular hypertrophy in the electrocardiogram from a man, aged 26, who has since had a successful operation. There is some left ventricular strain, as T is inverted in leads I and V6. He had pulmonary hypertension (78/54 mm.) and the R waves in V3R and V1 suggest some right ventricular hypertrophy as well. Standardization in the chest leads, half normal, 1 Mv.=0·5 cm. Case 22.

Case 23. A girl, aged 26, had to give up her work as a teacher. After an operation elsewhere the ductus recanalized and she could do very little. There was a typical continuous murmur and thrill, a loud pulmonary second sound, a pulmonary arterial pressure of 65/39, and a large heart (c.t.r. 59%) with some hypertrophy of both ventricles on radioscopy and in the cardiogram (Fig. 11).

A further difficult operation under hypothermia was thought to be her only chance. She seemed to be recovering but died the next morning with a nodal tachycardia (190 a minute). In addition to the very large pulmonary artery and ductus there was a small aneurysm of the aorta. Necropsy showed that the ductus had been closed; there was also coarctation of the aorta, the lumen being rather less than 1 cm. There were at least two areas of softening, about 1 cm. in diameter, in the internal capsule. We have no information about the condition of the smaller pulmonary arteries.

Case 24. A woman, aged 30, had always been a little short of breath but managed most of her housework. She had a collapsing pulse, a blood pressure of 155/59, and a very loud continuous murmur and thrill, perhaps with an independent diastolic murmur at the base. On catheterization there was a rise of O_2 saturation from 63 in the right atrium to 80 per cent in the right ventricle. The most likely diagnosis seemed a patent ductus with pulmonary regurgitation but a ventricular septal defect with aortic regurgitation could not be excluded. Operation was not advised as she was then pregnant for the second time: her confinement was normal. Three years later she was reasonably well and the physical signs were unchanged. Nothing was found that was incompatible with the diagnosis of patent ductus and in view of the large heart (c.t.r. 66%) operation has been advised.

There are, of course, patients even under 20 who show the urgent need for operation. A girl, aged 13, was fairly well until she developed bacterial endocarditis; during this illness the heart became larger and the blood pressure widened. There was gross left ventricular strain with T inversion from V4 to V6. The ductus was 15 mm. wide and rather fragile but was successfully closed. Some months later, her blood pressure was 110/70 instead of 135/30 and the heart was smaller (c.t.r. 55 instead of 67%).

Another girl, aged 14, was seriously disabled and had a large heart (c.t.r. 65%). There was such

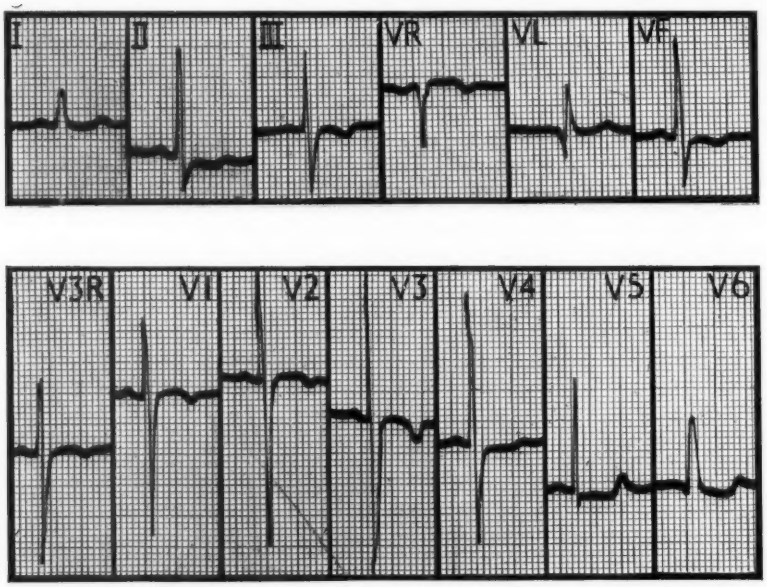

FIG. 11.—Biventricular hypertrophy from a woman, aged 26, with a large heart and increasing disability, where the ductus had been tied but had recanalized and left her with increasing symptoms. There are large R waves in V3R and V1, and the T waves are small or inverted in most leads. Standardization normal. Case 23.

striking pulsation that aortic incompetence was suspected, though the murmur was classical and catheterization confirmed the diagnosis, with a shunt that was 55 per cent of the left ventricular output: the pressure in the pulmonary artery was 60/46. When the ductus closed at operation it fell from 50/40 to 30/20, and at the same time, the pressure in the aorta rose from 60/44 to 104/68. She made a good recovery.

The progress of many of these patients can not be regarded as satisfactory and reinforces the argument that most patients with a patent ductus should have it closed while they are young. The question is dealt with more fully in the discussion.

III. Pulmonary Hypertension in Young Patients

In the older patients discussed so far the pulmonary arterial pressure was often normal and often somewhat raised. It can be very high even in young children and we have seen three girls between the ages of 3 and 6 years with systolic pressures between 70 and 87 mm. Hg. All three had classical continuous murmurs though this had not been recognized in the third where the quieter diastolic part and the loud split second sound made it difficult for some people to hear. This was probably due to the trivial aortic-pulmonary gradient during diastole (see Case 27) and soon she might have had a systolic murmur only. Two of the three had suffered since infancy from frequent " bronchitis " with asthma and pulmonary congestion—episodes that are very common with the larger left-to-right shunts. All had hypertrophy of the left ventricle and two some of the right ventricle also. The systemic flows averaged 4·2 and the pulmonary flows 11·8 litres a minute, which means that two-thirds of the left ventricular output was passing through the ductus, but this is no more than in many patients with a normal pulmonary pressure. All three have had successful operations and are much better and almost free from their bronchial attacks: the heart and the pulse pressure are smaller and the pulmonary arterial pressure has fallen to normal (Table V).

TABLE V

REDUCTION OF HIGH PULMONARY ARTERIAL PRESSURES AFTER OPERATION

Case No.	Sex and age	Shunt as percentage of LV output (%)	Heart size (c.t.r. (%))		Systemic blood pressure		Pulmonary aterial pressure		Pulmonary flow (litres/min.)	
			Before	After	Before	After	Before	After	Before	After
25	F6	66	59	51	100/50	110/80	87/50	22/6	14·5	6·0
26	F3	70	65	53	136/46	125/85	71/31	18/9	9·6	3·0
27	F5	54	60	55	110/55	100/70	73/46	30/19	11·2	3·6

Case 25. A girl, aged 6, was dyspnœic and had a continuous murmur, a loud pulmonary second sound, a large heart, and probably some right as well as left ventricular hypertrophy. Catheterization showed the pulmonary arterial pressure was 87/50 which was not much below the aortic pressure at that time, 100/50 mm. Nine months after a successful operation she was extremely fit: the pulmonary arterial pressure was 20/6 instead of 87/50 mm.

Case 26. A girl, aged 3, was very short of breath and had attacks like asthma since infancy. There was a continuous murmur, a loud pulmonary second sound, a large heart, and left ventricular preponderance. Nine months after the ductus had been closed she was very well and had kept without her respiratory infections: the pulmonary arterial pressure had fallen from 71/31 to 18/9 mm.

Case 27. A girl, aged 5, had often been in hospital with respiratory infections and pulmonary congestion, and was sent up as a case of atrial septal defect. She had a large heart and a continuous murmur which had not been recognized; R waves of about 8 mm. in V1 and of 7 mm. in V6 suggested hypertrophy of both ventricles. The pressure was 73/46 in the pulmonary artery at a time when it was only 85/47 in the aorta; five months after operation it had fallen to 30/19 mm.

These patients show that a high pulmonary pressure in young children is completely reversible, even when it is very high and not much below the systemic pressure (see discussion).

IV. Patients with a Balanced or Reversed Shunt from Infancy

Several of the patients already described have had a high pulmonary arterial pressure, in one high enough to reverse the shunt through the ductus after it had been in the normal direction for many years. There is, however, another group where it has been high enough from infancy or from an early age to produce a balanced or even a reversed shunt all the time. We have seen 6 such patients during the time that we have seen the 160 with the ordinary form of patent ductus.

All six showed physical signs of pulmonary hypertension, and this was confirmed by direct measurement (see Table VI): we think that the pressure had been raised since early infancy. Except for Case 28, none had evidence of a left-to-right shunt. These were the only patients in whom the pulmonary resistance was greatly increased, though it was somewhat increased in a few others. All six had right ventricular preponderance, and sometimes strain, while in the others hypertrophy of the left ventricle was the rule and hypertrophy of both ventricles was the most that was seen when the pressure rose. There was no general enlargement of the heart such as is common in complicated patent ductus, but this was not true of Case 31. All these patients showed polycythæmia and an increased hæmoglobin percentage, except Case 28 where we think that the shunt was balanced and Case 32 who was anæmic.

In the last four of these six the shunt was reversed, and the patient therefore showed cyanosis in the lower parts of the body and generally less cyanosis or none at all in the upper parts. In the first and perhaps in the second the shunt was generally balanced, and the diagnosis was made only after catheterization or angiocardiography. Although we think that Case 28 never had a continuous murmur and that her pulmonary hypertension dated from infancy, she should perhaps be included with the earlier patients as when she was 18 there was still a large left-to-right shunt through the ductus and no cyanosis was noted. Some months later when she was in Guy's Hospital the shunt was thought to be balanced but she was not recatheterized: the O_2 saturation was then 91 per cent

TABLE VI

SOME PHYSIOLOGICAL DATA IN PATIENTS WITH A BALANCED OR REVERSED SHUNT

Case No.	Sex and age	Heart size (c.t.r.) (%)	Hb. (%)	O_2: percentages				Pressures			Flows (litres/ sq.m./ min.)		Electrocardiogram
				RA RV	PA	Brachial	Femoral	RV	PA	Syst. art.	Syst.	Pulm.	
19*	F40	60	120	—	—	—	—	—	110/65	125/63	—	—	LVS and some RVH (Fig. 8)
28*	F19	55	84	51	79	91	90	99/7	108/72	125/75	—	—	RVS. T inverted V1–V4
29	F16	53	115	69	71	86†	—	95/0	95/65	105/80	4·2	2·8	RVP. T inverted V1
30	F38	51	130	55	53	72	—	59m.	100m.	140/10	?2·0	?1·5	RVS. T inverted V1–V5
31	F9	57	105	63	68	70	52	120/6	120/70	120/84	—	—	RVP. T inverted V1
32	F27	46	89	62	68	96	82	110/5	110/63	103/57	1·6	1·0	RVP. T late-rising in V2, V3
33	M10	48	135	47	47	—	44	66/12	66/52	66/48	—	—	RVP. T inverted V1

* Died after operation. † After breathing oxygen, 96 per cent.

in the left brachial and 90 per cent in the femoral artery. She is the only patient in this group where the ductus was closed: when this was done the pulmonary arterial pressure rose from 86/76 to 94/77, but at a second operation four months later it seemed to have fallen as it was 60/30 when the aortic pressure was 96/55 mm.

Case 28. A girl, aged 19, had not been allowed to play games but had few symptoms till she was 17. It was not possible to find out what murmur had been heard when she was 5 but when she was 13 she had a large heart, a basal systolic murmur, and a loud pulmonary second sound, and the consultant made no comment about any continuous murmur so it is unlikely that one had ever been heard. When she was 18, she had the same physical signs and right ventricular strain (R=S in V1 and T inversion from V1 to V4). After catheterization by the late Dr. J. L. Lovibond, operation was advised but Mr. Drew found the ductus so large that nothing was done.

Some months later she was admitted under Sir Russell Brock at Mr. Drew's request. The general condition was the same without any cyanosis clinically. At operation the ductus, 10 mm. long and 24 mm. in diameter at its narrowest part, was closed and she seemed better for some weeks, until she began to have pain in the chest, pyrexia, and hæmoptysis, when X-ray showed an aneurysmal dilatation above the left hilum which gradually increased. At a further operation under hypothermia, a large false aortic aneurysm filled the space between the aortic arch, the bifurcation of the pulmonary trunk, and the medial surface of the left upper lobe. It was dissected and the aorta sutured, but she died with recurrent ventricular fibrillation two hours later (Case 23, Milstein and Brock, 1954). Necropsy confirmed the observations made at operation, but no investigations of the pulmonary blood vessels were made.

Case 29. A girl, aged 14–19, had always been breathless but could walk 4 miles. She became cyanotic in winter but it seemed mainly peripheral. There was a rough systolic murmur, a faint thrill, and a loud and palpable pulmonary second sound, sometimes with a soft pulmonary diastolic murmur. She was thought to have a ventricular septal defect with pulmonary hypertension: most of her cyanosis was pulmonary in origin as the arterial O_2 saturation rose from 86 to 96 per cent. A small reversed shunt through the ductus was seen during angiocardiography though it had not been suspected clinically. Her condition has not changed much during five year's observation.

In the next four patients the shunt through the ductus was reversed, though it was not correctly diagnosed in the first till necropsy. No operation for closing the ductus has been advised as it was thought that their pulmonary hypertension dated from infancy and would prove irreversible, and

in others the disability did not seem great enough to justify operation with such a doubtful chance of improvement.

Case 30. A woman, aged 32–40, had cyanosis from birth and pulmonary hypertension and was thought to have Eisenmenger's complex with pulmonary regurgitation. When she died, however, necropsy showed that the ventricular septum was closed and that the right-to-left shunt was through the ductus from pulmonary artery to aorta. She has been fully reported (Campbell and Hudson, 1951).

Case 31. A girl, aged 9–11, was breathless but not much disabled. Her heart was enlarged and the cyanosis of her feet was enough for her mother to have noticed that it was present here but not in her hands. She has been fully reported by Cosh (1953: his Case 2).

Case 32. A woman, aged 27, had always been breathless but had been getting worse with recurrent hæmoptysis for five years, and had not been able to work for two years. She had always had some cyanosis on exertion and this was worse in the legs and feet than in the hands: there was slight clubbing of the toes but not of the fingers. There was a soft systolic murmur and a loud split second sound in the pulmonary area. The heart was not enlarged but the pulmonary arc was prominent. There was no evidence of a continuous murmur earlier though she had often attended hospital, the last time six years before for toxæmia of pregnancy. The arterial O_2 saturation was 96 in the brachial artery and 82 per cent in the descending aorta so there was a fairly large reversed shunt through the ductus.

Case 33. A boy, aged 10–12, had been cyanosed since he was a year old, and suffered from frequent chest infections. He could walk a quarter of a mile slowly, and cyanosis which had become worse recently was more obvious in the legs and feet. A diagnosis of mitral stenosis was made at an early age. There were loud presystolic and mid-diastolic murmurs in the mitral area, confirmed by phonocardiography, and a systolic murmur in the pulmonary area, where the second sound was loud and closely split. The left atrium was dilated and there was right ventricular preponderance with large pointed P waves in lead II. The reversed shunt through the ductus was confirmed by angiocardiography (Fig. 12) though the pressures

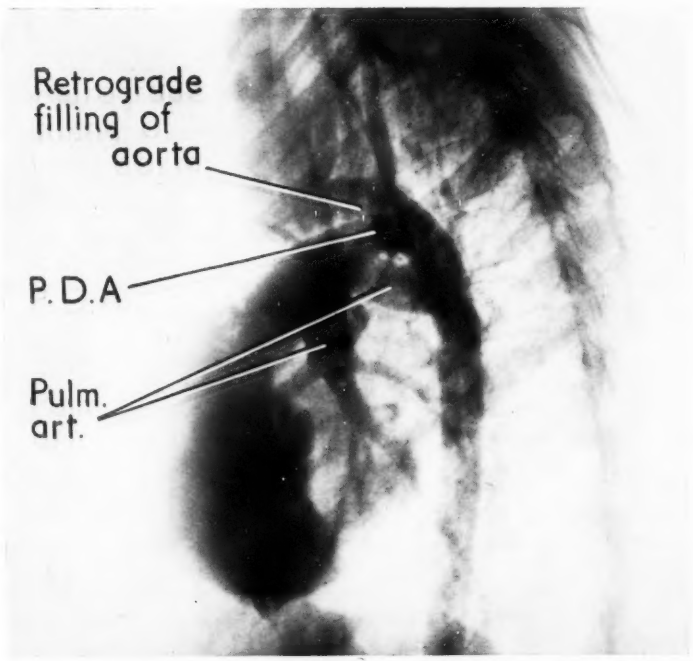

FIG. 12.—Angiocardiogram showing a reversed flow through the ductus with some retrograde filling of the aorta. Both pulmonary arteries are well filled. Case 33.

in the pulmonary artery and aorta were generally the same. The catheter provided no evidence of any left-to-right shunt and passed from the left pulmonary artery into the descending aorta.

His symptoms seemed to be mainly due to his congenital mitral stenosis. At operation the mitral valve itself was severely stenosed (3 mm. in diameter) and was made wider with an immediate fall in the left atrial pressure; there was also some narrowing of the subvalvular ring. In the two years since, he has been better and almost free from his winter coughs, but the shunt through the ductus is still reversed.

V. Discussion

Prognosis of Older Patients

This series shows that some patients are still doing well after 35 years but many are not. The first four (Cases 1–4) are without symptoms or any signs to suggest they are likely to get worse; in the first two the ductus is almost closed. Case 5 is 62 and was well until she was 50 but now has some dyspnœa, a large heart, and left ventricular strain. Case 7 had a large heart and Case 9 had left ventricular strain but neither has got worse in the subsequent four years and both are working without symptoms. These seven can be regarded as satisfactory and operation has not been advised in any of them though we think it should have been in Case 9.

Operation was advised but not accepted in four patients. The progress of the first two has not yet proved that it was needed though we still think it would have been wiser: in the other two there can be no doubt of the need. Case 6 was advised to have the ductus closed after her recovery from bacterial endocarditis because of her large heart, but she refused and has got on well for six years without any further increase of heart size. Case 8 has improved symptomatically over the four subsequent years but her heart has got larger (55 to 58%). Case 12 could do very little and has continued much the same. Case 20 got on fairly well for six years after operation was advised but then died with paroxysmal tachycardia and bacterial endocarditis. Paroxysmal tachycardia occurred in three patients who were doing badly and it seems, therefore, that it may be more serious prognostically than it usually is.

One patient died with a balanced shunt, the ductus not being recognized (Case 18). The other eight were becoming incapacitated and have had operations: all have been successful except the one in whom the shunt had become reversed (Case 19). Cases 10, 15, and 17 had been under observation for from four to seven years before this and were finding their ordinary days work increasingly difficult—a state of affairs that is well described by Gross (1952) in several middle-aged patients—sometimes with a progressive increase in the size of the heart or in the signs of left ventricular strain, though even at this stage the downhill course is often slow and further enlargement of the heart very gradual. Case 11 had a very large heart and left ventricular strain and was losing her continuous murmur from a rising pulmonary arterial pressure. Case 13 could no longer manage her work although the heart was not enlarged. Case 14 was quite incapacitated and had a very large heart. Case 16 had developed left ventricular failure and though she responded well to medical treatment it seemed unlikely that this would last long. In Case 19 the shunt had been reversed for nine months.

There does not seem to be any one indication for operation in middle-aged patients but progressive symptoms, a large heart, or increasing left ventricular strain, or all of these may show the need for operation. Some patients who developed these changes in the third decade (Cases 21–24) or even earlier have been described and reinforce the argument for early operation.

One can hardly read these cases and feel satisfied with the natural prognosis although most patients do well for so many years. It is true that this series is overweighted with those who are doing badly because they are more likely to come for advice, while those who are doing well are only seen by chance. To get a fairer impression the earlier patients should be multiplied several times and some of the later ones should be omitted because they were sent to us from outside the normal Guy's area, e.g. Cases 12 and 22 from India, Case 19 from South Africa when her shunt became reversed, and Case 23 because the ductus had recanalized. But even if these were omitted —and the others were all seen in routine hospital or private work—enough patients deteriorate

seriously during the third or fourth decades to suggest that all should have the ductus closed while they are young, when it can be done with a small risk.

The problem of a safe operation seems to me crucial. Most younger patients are so well that they will notice little improvement after operation: to their parents they appear normal children and they have an excellent prognosis for the next ten or twenty years. Many people are more interested in the near than in the distant future and this—not unreasonable—point of view can only be overcome by an operative mortality that is almost negligible.

Pulmonary Hypertension

The pulmonary arterial pressure is high in some patients with patent ductus but not in the majority (Dexter *et al.*, 1947). The reason is not obvious, for some may show a great increase within a few years (Cases 25–27), while others may show none though there has been a large flow through the ductus for 50 years (Cases 3 and 16). Thus Stortein *et al.* (1952) reported the case of a woman, aged 72, where the pulmonary pressure was only 44/22 mm. and our two oldest patients, aged 62 and 53, still had normal pulmonary pressures, 23/10 and 26/16: perhaps they reached this age because the flow through the ductus was not as large as some but it was 50 per cent of the left ventricular output. Some of these patients with large shunts who reach a good age without pulmonary hypertension develop left ventricular failure. This is supported by the pathological work of Welch and Kinney (1948) who found no increase of vascular sclerosis in 25 patients with large ductuses.

It is interesting to compare the frequency of a raised pulmonary arterial pressure at various ages. Shephard (1954) discussing the pressure-flow relationship in patent ductus found that of 20 patients under 25 years of age the pressure was normal (under 30 mm.) in 11 and increased in 9, the highest systolic pressures being between 50 and 60 in three children of 5 or under. Including these, we now have available figures for 54 patients. There were several where the systolic pressure was just over 30 mm. so we have included those up to 33 mm. with the normals (Table VII). The pressure was

TABLE VII

The Influence of Age on the Pulmonary Arterial Systolic Pressure

	Age in years				
	0–9	10–19	20–34	35 and over	All ages
Normal or nearly so (up to 33 mm.)	16 (3)*	4(2)*	7	5	32
36–60 mm. Hg	6	4	0	3	13
61–110 mm. Hg	3	1	2	3	9
With reversed shunts from infancy	1	3	1	1	6

* The figures in brackets are the number where the pressure was 31–33 mm.

normal in 20 and raised in 14 of those under twenty years of age and normal in 12 and raised in 8 of those over twenty years of age. In our 15 patients over 25 years of age who had cardiac catheterization, it was normal (up to 30 mm. systolic) in seven, aged 27, 30, 41, 44, 48, 53, and 60 years; moderately increased (36/13, 45/35, and 45/25 mm.) in three, aged 35, 35, and 38 years; and greatly increased (40 (mean), 65/39, 68/40, 78/54, and 110/63) in five, aged 35, 26, 45, 26, and 40 years respectively.

Chávez *et al.* (1953*a*) reported 40 cases of patent ductus with pulmonary hypertension, dividing them into three groups according to its degree. (1) Of 14 patients with slight hypertension, 31–60 mm., and typical continuous murmurs, half were children, aged 10 or less. (2) Of 14 with moderate pulmonary hypertension, 61–100 mm., nine were children of 11 or under, but four were

between 16 and 27: most still had continuous murmurs but four, including two children, had only systolic and diastolic murmurs. Half had electrocardiographic evidence of mixed right and left ventricular hypertrophy. (3) Of 12 patients with more severe hypertension, 101–136 mm., half were children of 10 or under, though four were between 16 and 33; and only one had a continuous murmur though five (including three children) had diastolic murmurs, generally best heard towards the apex. Most showed right ventricular preponderance and generally strain. In four, all under 17 years, the flow was reversed and in three, aged 3, 16, and 33 years, the flow was sometimes reversed and sometimes in the normal direction.

The authors thought that pulmonary hypertension was generally secondary to the patent ductus in adults but, partly because of the frequency with which they found it in children, that it was then of primary and unknown origin. This seems unlikely for the high pressure in children can generally be reversed by closing the ductus (see later) and is therefore caused directly or indirectly by the large pulmonary flow.

Age does not therefore seem to have much influence on the pulmonary arterial pressure. There is certainly no regular increase with age but the pressure may rise and systolic pressures over 60 mm. are found more often in adult patients. The pressure is still normal in more than a third of them and can be very high even in young children.

Pulmonary Arteriolar Resistance. In patients with a patent ductus the pulmonary resistance is generally low but we have found this less constantly than with atrial septal defect in children and this was also the experience of Wood (1950). In uncomplicated cases under 20, it is generally reduced to about the same levels as in atrial septal defect (0·5–1·4 units) but sometimes it is higher and reaches a normal or slightly increased figure. This applies to our three small children with the highest pulmonary pressures (Cases 25 to 27) and though the resistances were not much above normal before operation they have fallen to normal afterwards.

In patients over 20 years of age the actual resistance is distributed in much the same proportions between low, normal, and high (see Table VII), but this is hardly fair for the normal tendency is for it to become lower—240 at 5 years, compared with 120 dynes/sec./cm^5. at 20 years (Shephard, 1954)—so that there are a larger proportion with a pulmonary resistance that is normal or raised instead of being reduced: in most patients, however, including Case 3, aged 60, and Case 16, aged 53, it was still low. On the other hand, in Cases 10 and 15 it was normal and in Cases 11 (who was losing the diastolic part of the continuous murmur), 22, and 23, it was above normal but not very much: all these patients, except Case 11, were getting progressive symptoms and operation was advised in all of them. Shephard (1955) found that the pulmonary arteriolar resistance was often increased in adult patients: thus in the patients under twenty it was normal or reduced in 20 and increased in 3 only; on the other hand, in those over twenty, it was normal or reduced in 4 and increased in 5 patients.

The position was entirely different in the patients with a reversed shunt and in all of them the pulmonary resistance was enormously increased up to 15–30 units.

The statement that the pulmonary arteriolar resistance is increased does not, however, explain the problem and only raises another: why the arteriolar resistance should be so variable in different patients. The pulmonary flows are in the same general range in the patients with normal and in those with high pressures, but possibly an early rise of arteriolar resistance and pressure is a response to a flow that was at first unusually large.

Classification of Cases with Pulmonary Hypertension. Patients with a patent ductus and pulmonary hypertension appear to belong to two groups. (1) In the first the pressure has risen gradually as a result of the increased pulmonary flow. It is rare for the flow through the ductus to become reversed and when this happens (as in Case 19) it is only after a long period when the shunt has been in the normal direction. The diagnosis can be made on clinical grounds by the continuous murmur.

(2) In the second group the pulmonary arterial pressure has been high from birth or from early infancy. It has been suggested that the pulmonary hypertension is congenital in this group and this

view was accepted by Campbell and Hudson (1951) but it seems more likely that the arteriolar resistance and pressure rise unusually quickly because of the increased flow. The diagnosis may be suspected when there is pulmonary hypertension but can be made with certainty only by catheterization because they do not have a continuous murmur but only a systolic murmur, occasionally with a softer diastolic murmur of pulmonary regurgitation.

Group 1. There are not many reported cases with a balanced or reversed shunt where it can be said with certainty that they belong to this group. Holman (1925 and 1937) suggested that the shunt was reversed in many patients with cyanosis and right ventricular hypertrophy but probably the latter was secondary to pulmonary hypertension and the cyanosis was due to terminal failure and not to a reversed shunt. This view was taken by Wright and de Nevasquez (1942) in reporting the case of such a woman who died at the age of 57 years. Brown (1950) considers that reversal of the shunt is rare and with this we agree for Case 19 is the only certain one that we have seen, apart from those in Group 2.

A rising pulmonary pressure with the disappearance of the murmur in diastole, as in our Case 18, is more common and it is easy to see how such cases can be missed. There are many more where the pressure was rising to a level where this seemed likely in the future (e.g. Cases 11, 22, and 23) sometimes even in young patients (Cases 25–27).

The case of Harris (1955) certainly belongs to this group and probably Cases 6, 7, and 8 of Hultgren *et al.* (1953) and the case of Johnson *et al.* (1950) though a history of hæmoptysis when she was only 6 suggests pulmonary hypertension from infancy; in the last, however, there was still a left-to-right shunt and sometimes a reversed shunt through the ductus. It is difficult to be certain about some others partly because nothing is said about the presence or absence of a continuous murmur at an earlier stage.

Group 2.—Several patients who probably belong to this group have been reported recently. Among them are our Cases 28–33, some of the 4 cases of Alverez *et al.* (1950), the 3 of Cosh (1953), the 4 of Dammann *et al.* (1953), the first 4 of Hultgren *et al.* (1953), the cases of Novello *et al.* (1950), of Smith (1954), and of Emslie-Smith *et al.* (1955), and the 8 cases of Whitaker *et al.* (1955). If so, many of them stand the pulmonary hypertension well for years, for 16 of 23 were over 20 years of age and many did not have severe symptoms till the third decade. Even so it seems more likely that the woman aged 58 (Case 4 of Whitaker *et al.*) belongs to the first group and had an ordinary left-to-right shunt at first and developed pulmonary hypertension later.

The Reversibility of Pulmonary Hypertension. A high pressure in the pulmonary artery can revert to normal after the ductus has been closed. Thus in our three Cases 25–27 it fell from an average of 77/42 to 23/11 mm. Hg. This proves that the increased pulmonary flow is the cause, directly or indirectly, of the pulmonary hypertension. Other cases have been reported from time to time. Chávez *et al.* (1953*b*) reported two children aged 6 and 12 years where pulmonary arterial pressures of 68/41 and 104/63 fell to normal some months after operation, and Voci *et al.* (1951) reported one where it had fallen from over 50 to normal. In Case 7 of Hultgren *et al.* (1953), who was aged 33 years, it fell from 100/62 to 71/46 mm. one month after operation. Myers *et al.* (1951) reported two children where operations produced a good result although the pulmonary pressure was over 80 and near that in the aorta, but they were not recatheterized.

The fall of pulmonary arterial pressure may be immediate. Thus in our Case 27 it fell from 50/35 to 38/16 as soon as the ductus was closed, and in another child, aged 2, where it was 53/39 at catheterization, it fell from 64/44 to 36/14 at once. In one case of Bonham-Carter *et al.* (1955) it fell from 88/55 to 48/55 as soon as the ductus was closed. The observations of Cournand *et al.* (1949) suggest that pulmonary hypertension may be reversed even where there are structural changes in the lungs, for in one child a pressure of 60/36 was still 63/13 five weeks after operation, but had fallen to 32/5 after five months.

On the other hand, Chávez *et al.* (1953*b*) found some patients where the pressure had fallen considerably but not to normal. Thus in two children, aged 6 and 8, it had fallen from 109/68 to 51/11, and from 101/57 to 70/36; and in a patient of 27, from 69/36 to 40/14. Catheterization was

repeated after only two to four months so that the pressure might have fallen further. However, in a patient aged 33, where it was repeated after eleven months, it had fallen only from 103/57 to 59/30. The most disappointing patient was one aged 11, where it had risen from 103/57 to 145/74 after nineteen months, in spite of closing the ductus, but she may have belonged to Group 2.

It is important to know if equally good results can be obtained even after the flow through the ductus has become reversed: it seems that often it may be too late. Three of the patients of Chávez *et al.* (1953*b*) just quoted were greatly improved by operation though the shunts were sometimes reversed, and in another girl who has not been recatheterized, the result of closing the ductus has been excellent, although the systolic and diastolic pressures were 22 mm. and 12 mm. higher in the pulmonary artery than in the aorta. Against these favourable cases there were three deaths: a girl of 16, cyanotic from birth, with a pulmonary pressure of 136/68, died at once from a tear in the pulmonary artery; a woman, aged 30, with a pulmonary pressure of 103/76 and a reversed shunt died two days after operation with acute cor pulmonale; and a child died some hours after operation with severe disturbances of the heart rhythm. Death followed closure of the ductus in the case of Smith (1954) although the pulmonary pressure became lower when it was occluded, and in a case reported by Novello *et al.* (1950) and in our Case 19. Case 1 of Dammann *et al.* (1953) died at operation before the ductus had been ligated. The case of Johnson *et al.* (1950) died five days after operation but the ductus had recanalized. There are, however, not enough reported cases to prove the pressure is irreversible even at this late stage and it seems that every case, whether successful or not, should be recorded for the present.

These patients show that a high pulmonary pressure can fall when the ductus is closed, as it does after a successful mitral valvotomy; this means that there are, as a general rule, no irreversible changes in the pulmonary arteries. The speed with which it can fall shows that in many cases there are no structural changes in the pulmonary arteries, though there is some evidence that, even when there are such changes, they may still be reversible.

On the present evidence it is unwise to assume that pulmonary hypertension is irreversible in any *child* with a patent ductus. The unusually high pressures seem to be an individual response to a large flow and not an independent pulmonary hypertension dating from birth. We think that every uncomplicated patent ductus should be closed, unless there is evidence that it is already closing, but agree with Chávez *et al.* (1953*b*) that where the pulmonary pressure is so high that the shunt is reversed, there are great dangers in either course and, ideally, it should have been closed earlier before the pressure had risen so high.

Summary and Conclusions

Some patients with a patent ductus arteriosus may show a diminishing murmur and a freedom from signs and symptoms that shows the ductus is almost or completely closed. A few with classical signs and a large shunt may reach 50 or 60 years of age with few symptoms. Many, however, get increasing symptoms, a larger heart, and left ventricular strain about the fourth decade, and may develop heart failure. Probably more than have been recognized develop a balanced shunt and lose the murmur in diastole, but reversal of the shunt is rare, though possible.

The exact proportions in these groups could be settled only by following up a series of cases seen from childhood and this would have to be done for thirty years since most children make good progress with few complications for many years. We have described 20 patients over 35 years and it seems from these and from other reports that the number deteriorating in the third or fourth decades is a valid reason, quite apart from the risk of bacterial endocarditis, for advising that all patients should have a patent ductus closed, unless there are reasons for thinking that it is closing spontaneously.

The pulmonary arterial pressure is very variable. It is often normal but may rise to high levels even in young children of 3 years or less; it may rise as the patient gets older or it may still be normal though there has been a large shunt through the ductus for 60 years. In younger patients a high pulmonary arterial pressure can certainly be reduced to normal by closing the ductus and is a reason

for operation rather than a contra-indication. So far there are few successful operations and several deaths in patients where the pressure has risen enough to reverse the flow, but in children at any rate the possibility of success should not be neglected.

There is, however, another group where the pressure has risen in infancy and the flow has been balanced or reversed since then. We have seen 6 of these cases during the time that we have seen 160 ordinary cases. If these patients are not seen till many years later, it seems too late to reverse the high pressure by closing the ductus, since there may be a high pulmonary arteriolar resistance and extensive structural changes in the pulmonary arterioles. If, however, they are recognized early, this may not be true, for they may be essentially the same as the others and differ only because an unusually large flow has led to a rise of pulmonary arterial pressure in infancy.

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CONTROL OF QUINIDINE DOSAGE

BY

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The usefulness of quinidine in treatment of cardiac arrhythmias is often limited by the difficulty of determining adequate dosage. When control has not been effected by small doses, the physician may be deterred from increasing these because of the risk of toxicity. The electrocardiogram does not help to indicate that this may be imminent, since the effects of overdosage (widening of QRS and ventricular arrhythmias) are preceded by the clinical evidence of intolerance—vomiting and tinnitus.

In 1943 Brodie and Udenfriend described a fluorimetric method of estimating quinidine in serum. Subsequently it has been demonstrated that the therapeutic and toxic effects of the drug are related to serum concentration. Kalmanson and Sampson (1949) showed that toxic phenomena occurred more frequently with levels above 0·6 mg./100 ml. than with lower concentrations. Sokolow (1951) found that the majority of conversions from auricular fibrillation to sinus rhythm took place at levels between 0·4 and 1·0 mg./100 ml. Where such levels had not been reached, dosage could be increased with safety and with the possibility of therapeutic success. Above 1·0 mg./100 ml., the chances of conversion are only slightly enhanced, while the risk of toxicity is much increased.

In the present investigation, the relationships between dosage, serum level, and therapeutic effect were studied. The urinary excretion of quinidine was studied also, and the urines were tested with potassium mercuri-iodide (Tanret's reagent) to determine whether precipitate density was any guide to serum level. Tanret's reagent has been used hitherto to detect the presence of *quinine* in urine, either to ensure that prophylactic doses were actually being taken, or to determine whether quinine used therapeutically was being absorbed (see Howie and Murray-Lyon, 1943; and, for a quantitative method, Lipkin and Ramsden, 1918).

Material and Methods

Seventeen patients were investigated. In thirteen there was auricular fibrillation, which was paroxysmal in four cases. One patient had persistent auricular flutter and there were three with paroxysmal tachycardia. Of the patients with fibrillation, one had essential hypertension and three had mitral valve disease; in one of these the arrhythmia first appeared after valvotomy. One case of paroxysmal tachycardia started following cardiac infarction. The case with flutter had an atrial septal defect and flutter became established after cardiac catheterization. In the remaining eleven there was no other evidence of cardiovascular disease. Quinidine sulphate was always given by mouth, usually at two-hourly intervals for between three and six doses daily. The total daily dose used ranged from 15 to 45 grains (1 to 3 g.), but in addition studies were made in four patients after a single dose of 10 grains (0·7 g.). In each case, samples of blood and urine were obtained immediately preceding each dose of quinidine, and at intervals after the day's last dose, for a total period of 24 hours.

Estimation of Quinidine in Serum. To 39 ml. of distilled water 1 ml. of serum was added in

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a 100-ml. centrifuge tube, and mixed; 10 ml. of 20 per cent metaphosphoric acid were added with vigorous shaking to avoid occlusion of the quinidine by the protein precipitate, and allowed to stand for 15 minutes. The mixture was centrifuged at 2000 r.p.m. for 10 minutes and the clear supernatant liquid decanted. This solution is sufficiently acid to give maximum fluorescence. The fluorescence was then measured in the Hilger Spekker photoelectric fluorimeter, by comparison with the appropriate standard. A description of the instrument and technical procedure is given by Lothian (1942). A pair of Wood's glass filters were used to isolate the mercury line 365°A. In front of the photocell on the left a neutral filter H508 was placed to block stray visible light from the photocell. A heat-absorbing filter was placed on the left of the lamp house. In front of the photocell on the right there was mounted a filter to absorb ultraviolet light that might be scattered in the solution.

The stock solution was quinidine sulphate 10 mg. in 100 ml. of *N*/10 sulphuric acid. From this, working standards of 0·1, 0·05, 0·025, and 0·0125 mg. per 100 ml. were prepared by diluting the stock with 4 per cent metaphosphoric acid. When kept in a refrigerator the stock standard keeps indefinitely and the 0·1 mg. standard for several weeks. Weaker standards will keep for a few days. There is no difference in fluorescence between standards prepared with *N*/10 sulphuric acid and 4 per cent metaphosphoric acid. Deproteinized filtrates from the serum of patients before administration of quinidine may be used for the preparation of standards, but such quinidine-free serum was not usually available. The highest concentration for which a linear relationship could be obtained was 0·2 mg. per 100 ml. The greatest accuracy was obtained when the standard used was 0·05 mg. per 100 ml. The test is compared with the appropriate standard and the ratio of the two fluorescence intensities determined. The conversion factor for quinidine sulphate to quinidine is 0·8287.

We confirmed Edgar and Sokolow's (1950) findings that blood may be stored for several days without loss of quinidine. The protein-free filtrate retains its fluorescence for up to a fortnight.

Estimation of Quinidine in Urine. In a 50-ml. separating funnel 10 ml. of protein-free urine was placed and made alkaline with 1 ml. of 2·5*N* NaOH. The extraction was carried out with 15 plus 10 plus 10 ml. chloroform by shaking gently each time for one minute. Each chloroform extract was run into a second 50-ml. funnel and washed twice with 5 ml. of water which is then separated by aspiration. The same two portions of washing water were used for all extractions. The combined chloroform extracts were evaporated to dryness in a 100-ml. porcelain dish on a waterbath. The residue was dissolved in 100 ml. 4 per cent metaphosphoric acid, using several portions and swirling the acid well all round the dish. The fluorimetric estimation is then carried out as for serum, diluting as necessary with 4 per cent metaphosphoric acid, using the same standards. Should the urine contain excess phosphate, preliminary removal with barium chloride is advisable. Recovery experiments showed complete recovery when quinidine sulphate was added to serum. With urine, the addition of quinidine sulphate to concentrations of between 5 and 80 mg. per 100 ml. resulted in recovery of from 95 to 101 per cent.

The Tanret Test. The reagent was prepared by dissolving 1·36 g. of mercuric chloride in 70 ml. of water, and 5 g. of potassium iodide in 20 ml. of water. The two were mixed and the volume made up with water to 100 ml. (Martindale, 1935). During mixing, an orange-red precipitate forms, which redissolves. The reagent turns yellow with the passage of time, from liberation of iodine, without affecting it for the purpose of this test. 5 ml. of clear urine (filtered if necessary) were placed in a test-tube and 5 drops of reagent added. This was found to ensure complete precipitation. The tube was shaken by inverting it a few times and the density of precipitate noted. The reagent as specified here is best for this test, since it produces a fine suspension. If the alternative formula with acetic acid be employed, coarsely granular precipitates are formed which settle too rapidly for interpretation. The precipitate density was recorded as " nil," " trace," " one plus " (an opacity through which print could be read) or " two plus " (a completely opaque tube).

Tanret's reagent is also precipitated by other alkaloids and by methonium salts and procaine amide; hence the test cannot be used in patients having these drugs. Other substances routinely used in cardiovascular disease were found not to be precipitated; these were digitalis, tromexan,

dindevan, mercurial diuretics, penicillin, and sulphonamides. Their use concurrently with quinidine does not invalidate the test. Albumin gives a false positive, but the precipitate persists on heating while that due to quinidine (or quinine) disappears, to return on cooling. Should albumin be present the urine must be heated with acetic acid and then filtered and cooled before adding Tanret's reagent.

Results

After a single oral dose of 10 grains the highest serum level found was about 0·5 mg./100 ml. (see Fig. 1). This peak was reached from two to four hours after ingestion, as found by Delevett and Poindexter (1946). With repeated doses, the level rose until a maximum was reached two hours after the last dose (Fig. 2), confirming the findings of Sokolow (1951). When dosage was continued for several months, the serum level remained round about a steady level throughout the

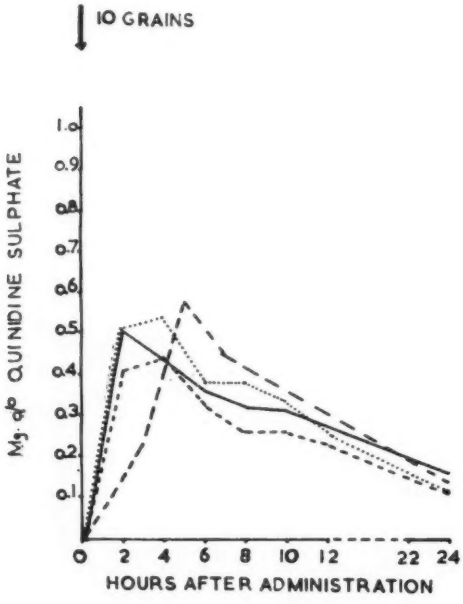

FIG. 1.—Serum levels in four patients after 10 g. of quinidine sulphate.

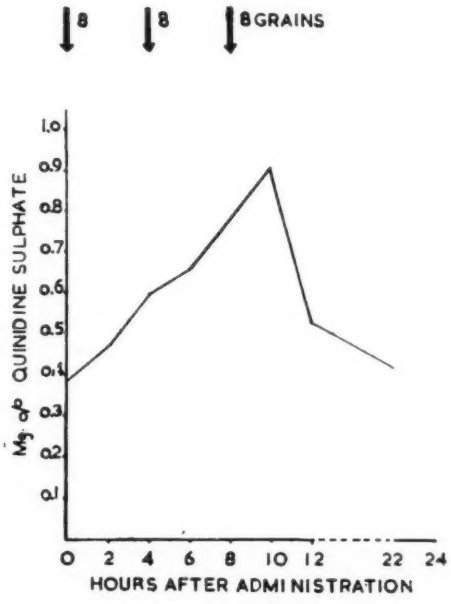

FIG. 2.—Peak serum level is reached two hours after the final dose. The initial level is due to previous day's therapy.

twenty-four hours (Fig. 3). The values in this paper are for quinidine sulphate and represent 80 per cent of the corresponding figures in American reports, in which results are expressed as quinidine base.

The maximum levels found in all cases are shown in Fig. 4. While these generally were higher with larger doses, there was a wide range in different patients having identical amounts. Two factors were possibly responsible for this. One was the variation in the number of days of treatment prior to the day on which the estimations were made, since cumulation occurs (Gold, 1946; Sokolow and Edgar, 1946). The other was the variability in the percentage of quinidine that was excreted in the urine.

As is seen from Fig. 4, most of the therapeutic successes took place at or above the level of

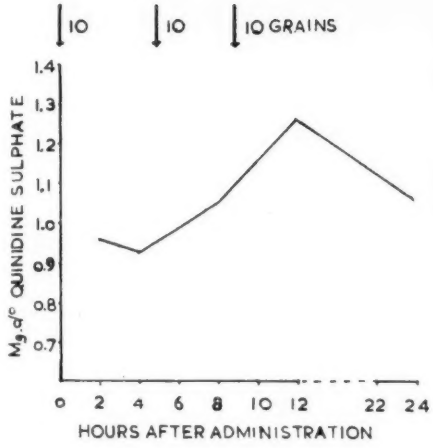

FIG. 3.—Relatively steady serum level in a patient who was on a constant daily dose of quinidine for some months.

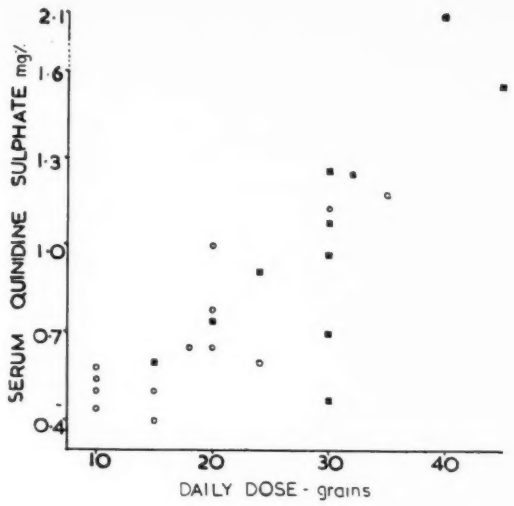

FIG. 4.—Peak levels in all cases in this series, according to dose. The black squares denote reversion to sinus rhythm; and the circles, persistence of arrhythmia.

0·7 mg./100 ml. Conversion to sinus rhythm occurred in 61 per cent of patients with such levels, as compared with 18 per cent of those with lower concentrations. In two cases that failed to respond to daily totals of 20 and 24 grains respectively, the highest serum levels were 0·60 and 0·65 mg. These showed that larger doses were safe and worthy of trial. Sinus rhythm was restored in both cases with a daily dose of 30 grains, with levels of 0·7 and 1·08 mg. respectively. In four other cases that did not respond, serum levels ranging between 1·0 and 2·1 mg./100 ml. were considered to contra-indicate any increase in dose in view of the risk of toxicity.

Individual variance in drug tolerance was seen. In four patients there was no evidence of toxicity at levels of 1·13–1·56 mg./100 ml., while two others developed cinchonism at 1·08 and 1·18 mg./100 ml. The highest level found was 2·1 mg., in a patient with hepatic cirrhosis given 45 mg. in four hours. He became very nauseated and disorientated.

In seven patients in whom the 24-hour urinary output of quinidine was determined, the excretion varied from 9 to 34 per cent of the amount ingested. This variation bore no relation to the volumes of urine passed. These findings confirm those of Houston and Perry (1950) and Sokolow and Edgar (1946) who recovered fractions ranging from 1 to 30 per cent. It was because of this variability that no useful information is obtained from any attempt to make the Tanret reaction a quantitative test.

The results obtained with the Tanret test are shown in Fig. 5. There is a fair degree of correlation between serum level and precipitate density in the high and low ranges but considerable overlap with levels between 0·4 and 0·7 mg./100 ml. In addition to this the test was materially affected when the volume of urine passed was unusually small or great. Samples of 150 ml. or less gave dense opacities even when the serum level was 0·4 mg. or under, whereas with large volumes (300–600 ml.), " trace " or " one plus " precipitates were found even with serum levels of 0·8–1·0 mg. In each patient both Tanret opacities and urinary quinidine levels ran parallel to changes in blood concentration (Fig. 6); but opacities and urine levels varied in relation to the blood concentrations found in different patients.

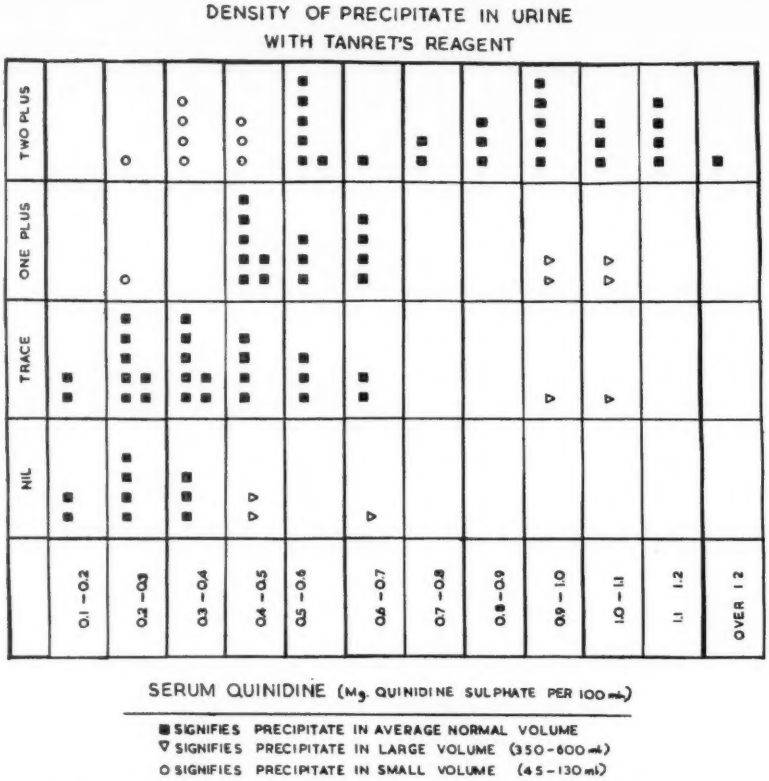

FIG. 5.—Comparison of serum quinidine levels with density of Tanret precipitates.

TABLE I
INTERPRETATION OF THE TANRET TEST

	Urine volume less than 150 ml.	Urine volume 150–350 ml.	Urine volume over 350 ml.
Tanret negative	Serum level under 0·4 mg./100 ml. Increase dose	Serum level under 0·4 mg./100 ml. Increase dose	Unreliable. Repeat on different specimen
Trace	Serum level under 0·4 mg./100 ml. Increase dose	Serum level under 0·7 mg./100 ml. Increase dose if necessary	Unreliable. Serum level at least in therapeutic range
One plus	Unreliable. Serum level may be under 0·4 mg./100 ml. Safe to increase dose	Serum level in therapeutic range. Safe to increase dose	Serum level high (0·8 mg./100 ml. or over). Caution
Two plus	Unreliable. Repeat on different specimen	Serum level may be high (0·8–1·0 mg./100 ml.) Caution	Serum level high. Caution

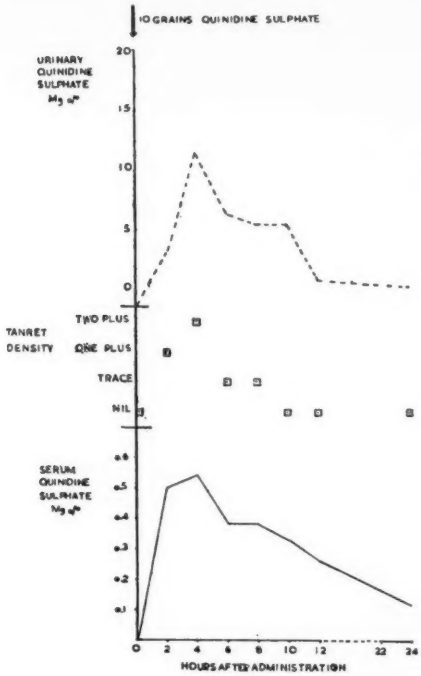

FIG. 6.—Simultaneous serum quinidine levels, Tanret precipitates, and urine quinidine levels in one patient.

DISCUSSION

These results confirm the findings of American workers concerning the usefulness of serum quinidine determinations for regulation of dosage. Where the desired effect has not been achieved, the serum level indicates whether or not it would be safe or advantageous to increase the dose. Since this method requires special apparatus and laboratory facilities, it was hoped that the Tanret test would furnish an alternative empirical guide. The accuracy of this test is, however, limited by the variability of quinidine excretion, by the influence of sample volume on precipitate density, and by the equivocal results obtained with serum levels of 0·4–0·7 mg./100 ml. Provided that these limitations be recognized, however, the test can often give useful information. Table I shows how interpretation of the Tanret test is modified by the volume of the specimen. It will be seen from the Table that the following deductions can be drawn:

(1) With a small volume of urine, only a negative result (or a trace) is significant.

(2) With a large volume, only a definite precipitate is significant.

(3) With intermediate volumes (150–300 ml.), a negative Tanret indicates a serum level below 0·4 mg./100 ml., and control of the arrhythmia is unlikely unless the dose be increased. With a trace or " one plus " precipitate the serum level is unlikely to exceed 0·7 mg., and the dose may safely be increased if necessary.

(4) The finding of a dense precipitate in a specimen of 200-ml. volume or more indicates a high serum level and caution in dosage is necessary.

These statements apply not only to decisions concerning the daily total dose, but also to the number of doses to be given on any single day, since the urine can be tested two hours after each dose to ascertain if further doses are advisable. Clearly, any symptoms of intolerance contra-indicate further quinidine irrespective of serum level or Tanret test.

Gold (1946) and Sokolow and Edgar (1946) showed that with a fixed daily total, there was cumulation up to 72 hours; after this the serum level did not rise further unless the dose were increased. Hence there is no point in continuing any given dose level for more than this time if there is no response. Similarly if the effective dose does not give rise to toxicity within this time it may be safely continued (Gold, 1950). These findings were confirmed in the present series.

Summary

Serum and urinary quinidine levels were estimated by photofluorimetry in 17 patients under treatment for cardiac arrhythmias. The methods are described in detail.

With routine doses, serum levels in the therapeutic range (0·4–1·0 mg./100 ml.) were attained.

The urine of subjects taking quinidine gives a positive Tanret reaction. This test was used as a guide to regulation of dosage.

We are indebted to Dr. Graham Hayward, at whose suggestion the study was undertaken, for advice and criticism. The patients were under the care of the Physicians to the National Heart Hospital.

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RUPTURE OF ANEURYSM OF AORTIC SINUS (OF VALSALVA) INTO THE RIGHT SIDE OF THE HEART

BY

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We were fortunate enough to see two examples of rupture of a sinus of Valsalva into the right side of the heart within a few months of each other, and were so struck by the similarity in the clinical pictures that we looked up the recorded cases to see whether the syndrome presented by our patients was at all common. We have attempted to study the incidence of clinical findings that might serve as a guide to recognition of the syndrome in the future.

The clinical diagnosis of our first case was confirmed by catheterization and was so likely that surgical correction was attempted. The second patient was too ill to permit of catheterization, but again a confident clinical diagnosis was made and subsequently confirmed at autopsy. In spite of failure to correct our first case surgically, from a study of the nature of the rupture its repair should prove feasible if a heart–lung machine is available, particularly as following a small rupture, such as our first case showed, the patient may live for several months.

Although there are many anatomical descriptions of aneurysms of one or more sinuses of Valsalva, the number of cases in which rupture has occurred is not great. We have considered only those cases of rupture that have lived long enough to develop symptoms and signs, and, with one exception, we have ignored those where no autopsy confirmation was available. The case in which no autopsy was made but where the diagnosis seemed to us to be irrefutable is that of Arias and Baudino (1952). Including our own two cases we have been able to find 23 convincing examples of the syndrome. It seems very doubtful whether previously the diagnosis has been made in life, although a few authors state that it was suspected among other possibilities.

The suggestion that such a diagnosis during life is feasible is usually attributed to Maude Abbott (1919) but she herself states that the clinical features of abnormal communication between a sinus of Valsalva and the right side of the heart were first clearly outlined by Thurnam in 1840. As a matter of historical accuracy precedence should be given to James Hope who, in the third edition of *A Treatise on Diseases of the Heart and Great Vessels*, published details of Thurnam's case a year earlier.

Case Reports

Case 1. H.R., aged 36, walked into the Out-Patient Department and said that five weeks before, while straining at stool, he suddenly became aware of his heart beating rapidly and two or three minutes later developed a pain across the front of his chest. This pain became increasingly severe during the night and then gradually lessened, and although it was present for three days, he attempted to cycle to work on the second day, but had to return home because of severe dyspnœa. A few days after his attack of pain he developed a cough which was still present on examination. After three weeks he noticed his ankles and legs had become swollen and this had persisted. He had required an increasing number of pillows in bed to help ease his dyspnœa.

Until his attack he was perfectly fit and served in the army during the Second World War in a low category on account of defective eyesight and flat feet. There was nothing significant in his family history.

On examination he looked very ill with a pale sweating face, lilac-coloured lips, blue hands and feet, and obvious dyspnœa on slight exertion and even on talking. His jugular venous pressure was very high and systolic venous pulsation could be seen not only in the neck veins but even extending up the temporal region to the scalp. His pulse was strikingly collapsing, 94 a minute, and dropped beats were present. Femoral pulsation was easily palpable and a pistol-shot sound was audible over the femoral arteries. The systolic blood pressure was 170 and the diastolic figure varied from 60 to nought. Capillary pulsation was easily discernible in the nail beds. His apex beat was displaced almost to the anterior axillary line and was diffuse and weak. A teleradiogram showed considerable generalized cardiac enlargement associated with congestion of the pulmonary circulation, but without any decisive diagnostic features. A thrill was palpable both in systole and diastole over the mesocardium. There was a very loud whirring murmur of peculiar quality, to and fro in type, with systolic accentuation and heard best near the centre of the sternum. The pulmonary second sound was loud and single. There were crepitations at the bases of both lungs. His liver was four finger-breadths enlarged and systolic pulsation was palpable. There was considerable œdema of his ankles and a large lumbar pad.

The electrocardiogram showed strikingly low-voltage limb leads, both standard and unipolar, and there was slight depression of the RS–T segment in leads VL, I, and II. Similar depression and low voltage was present over the left ventricle (leads V5 and V6). The P–R interval varied in length progressively until a beat was dropped, giving rise to Wenckebach periods. There was no evidence of cardiac infarction.

The Wassermann and precipitation reaction were negative. The urine was acid in reaction, with a moderate cloud of protein, a moderate number of leucocytes (6–30 per H.P.F.) and occasional red cells. Small numbers of hyaline casts and an occasional granular cast were present. The sedimentation rate was 2 mm. in the first hour (Westergren).

Cardiac Catheterization. This was performed by Dr. Peter Harris. The findings are quoted in some detail, as, to the best of our knowledge, the only other patient that has been catheterized is that of Arias and Baudino (1952) but unfortunately in their case a persistent left superior vena cava was suspected and there was no confirmation of the diagnosis at autopsy.

It will be seen (Table I) that there was a considerable increase in oxygenation of the blood as it reached the right atrium and a further significant rise on entering the right ventricle. At the time this was interpreted as indicating a shunt of arterial blood into the right ventricle with severe tricuspid incompetence. The blood in the femoral artery was normally oxygenated. Oxygen consumption was not measured and estimations of flow were therefore not possible.

TABLE I

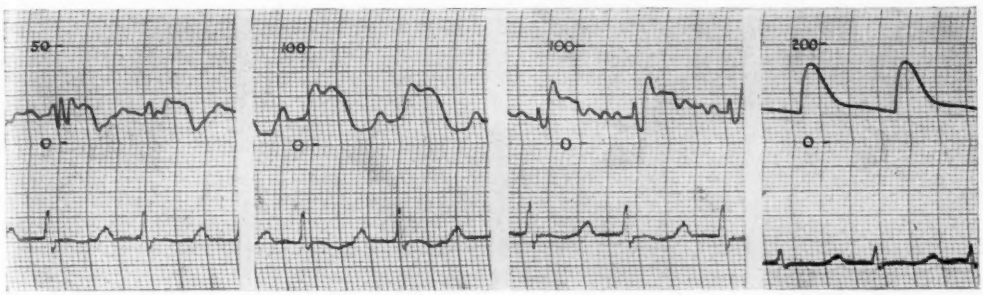
CARDIAC CATHETERIZATION

Site	Systolic pressure	Diastolic pressure	Oxygen content (vols. %)	Oxygen saturation (%)
Superior vena cava	—	—	15·0	73
Inferior vena cava	—	—	10·0	49
Mean vena caval	—	—	12·5	61
Right atrium*	—	—	17·0 16·7	82·5 81
Right ventricle inflow	55	start 13 end 25 "A" wave 35	18·1	88
Right ventricle outflow	47	start 8 end 20 "A" wave 30	18·1	88
Pulmonary trunk†	51	27	18·1	88
Right pulmonary artery	62	38	18·5	90
Left pulmonary artery	52	27	18·5	90
Right femoral artery	160	60	20·0	97

* Mean pressure 11 mm. † Mean pressure 36 mm.

Pressure readings in mm. Hg from table level; means by planimetry. Blood samples: hæmoglobin 15·4 g./100 ml., therefore oxygen capacity=20·6 vols. per cent.

The right atrial tracings (Fig. 1A) showed a group of vibrations due to the first heart sound immediately following the QRS complex of the cardiogram. After the first sound there was a prolonged systolic wave in the auricle. This wave was presumably due to the influx of blood into the right auricle from the aorta. At this point in the cycle the shunt of blood would be greatest, and at the same time the A-V valves would be closed so that the pressure in the right auricle would be expected to rise. A similar appearance could have been caused by tricuspid incompetence. The systolic wave in the right auricle ended with a sharp descent which, on superimposing the right ventricular tracing (Fig. 1B) could be seen to coincide with the end of the descending limb of the right ventricular systolic pulse wave and, therefore, with the opening of the tricuspid valve.



A B C D

FIG. 1.—Pressure tracings. (A) Right atrium. (B) Right ventricle. (C) Pulmonary artery. (D) Femoral artery. See text for description. Case 1.

There was a greater interval than is usual between the right auricular *a* wave and the vibrations of the first sound owing to the delay in A-V conduction. In the right ventricular tracings the *a* wave was unusually prominent. This prominence of the *a* wave in the right ventricle together with the rather steep rise in the right ventricular pressure during diastole might have indicated a lack of distensibility of the right ventricle due to dilatation. The steepness of the rise would also be enhanced by the increased flow of blood due to the shunt. The pressure in the pulmonary artery was above normal (Fig. 1C). No adequate tracing of pulmonary artery wedge pressure could be obtained. The tracings from the femoral artery (Fig. 1D) showed an abnormally wide pulse pressure which, in the absence of aortic incompetence, was taken to indicate that the aorta was the origin of the intracardiac shunt.

Progress and Treatment. The patient continued on digitalis, and was given a sodium restricted diet and mersalyl, to which there was a poor response.

A diagnosis, as a result of clinical and catheter findings, of rupture of an aneurysm of a sinus of Valsalva into the right side of the heart having been made, Mr. W. Cleland was asked to see the patient with a view to possible surgical repair of the rupture. He was transferred to the Hammersmith Hospital ten days later. He became progressively more uræmic and his blood urea reached 151 mg. per 100 ml. In milli-equiv./litre the serum bicarbonate was 25·6, sodium 127, potassium 5, and chlorides 91. At first his condition improved, but he became very salt deficient and had to have added salt, and he was maintained in electrolyte balance by daily estimation until operation.

At operation, seven weeks after his admission, the aneurysm was seen as a small projection very close to the A-V ring. Two communications between the aneurysm and the right side of the heart were present, one opening into the right auricle and the other into the right ventricle. The auricular communication was successfully ligated with difficulty owing to the friability of the tissues, and at this point 2 : 1 heart block developed, and finally the heart stopped, and although it re-started after cardiac massage it finally stopped beating in spite of use of the heart–lung machine.

Post-mortem Findings. The heart weighed 333g. The aneurysm was found to be arising from the base of the right coronary cusp of the aorta and had opened into both the right auricle and ventricle above and below the A-V ring. The auricular portion had been closed successfully by sutures (Fig. 2A) but there was still a small opening into the right ventricle. The aneurysm was saccular and measured 12 mm. in diameter and was about 15 mm. in depth, and the walls were quite smooth (Fig. 2B). The aortic valve cusps were normal macroscopically and showed slight fenestration. The ventricular septum was intact.

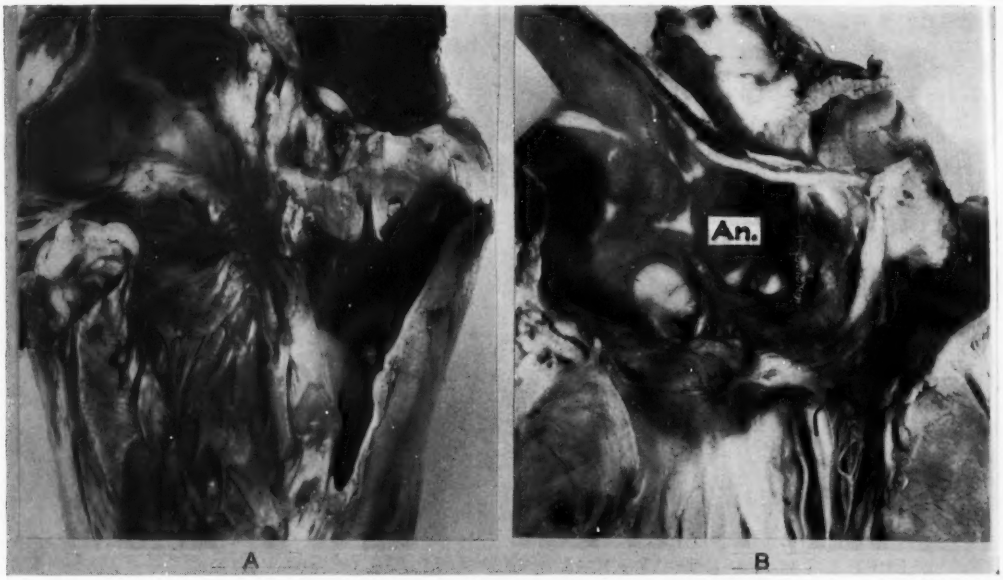


FIG. 2.—(A) Interrupted sutures of black thread just above the origin of the tricuspid valve mark the site of rupture of the aneurysm into the right auricle. The perforation of the aneurysm into the right ventricle cannot be seen. (B) The cavity of the aneurysm (An.) can be seen as a triradiate impression above the right coronary cusp of the aortic valve. Fine fenestration of the aortic valve is visible. Case 1.

Histological examination of the valve cusps, the aneurysm in the region of the rupture, and the aorta was made, and no cause for the rupture was apparent; in particular no evidence of syphilis was found. Section of the kidneys showed no significant abnormality.

Case 2. E.L., aged 67, was quite well until one morning when he awakened at 2.30 a.m. with sudden very severe pain which he described as feeling as though the upper part of his chest had been struck with a cricket bat. The pain decreased gradually and within six hours had become only slight in intensity. He had a small breakfast and walked to catch his train, but found that he was very breathless even on walking, and had to return from his office after less than an hour because he felt so ill. The following day he experienced a momentary needle-like pain in the left of his chest. His past history, which was obtained from his son, suggested that he might have suffered previously from attacks of paroxysmal tachycardia. There was nothing significant in his family history.

On examination he was an ill-looking orthopnœic man with fairly deep cyanosis. His pulse was collapsing, rate 104, and auricular fibrillation was present. His blood pressure was 150/60. The jugular venous pressure was raised, and his jugular veins and lingual veins were engorged and showed systolic pulsation. His liver was enlarged about one hands-breadth and also showed systolic pulsation and was slightly tender. There was a right-sided pleural effusion, a small sacral pad of œdema, and some ascites, but no œdema of the ankles. His apex beat was in the anterior axillary line in the fifth space and the cardiac impulse was diffuse. The pulmonary second sound was somewhat loud, and there was a peculiar continuous murmur which, although widely heard, was not particularly loud and was heard best just to the right of the mid-sternal region and had systolic accentuation. No thrill was palpable. A teleradiogram of the chest confirmed the right-sided effusion; the heart was displaced a little to the left and showed moderate enlargement but its outline was not sufficiently clear to judge its size accurately.

The electrocardiogram showed auricular fibrillation with some digitalis effect on the RS–T segment; there was no axis deviation nor was there evidence of cardiac infarction. The sedimentation rate was

5 mm. in the first hour (Westergren). The *white blood count* was 15·9 thousand (neutrophils 76%, lymphocytes 10%, monocytes 14%). The serum sodium was 300 mg.; serum potassium 22·6 mg.; plasma chloride 351 mg.; and the blood urea 345 mg. each per 100 ml.

Progress and Treatment. In spite of digitalis and a low salt diet and venesection of one pint he deteriorated rapidly and developed a chronic frequent non-productive cough. Slight jaundice then appeared and he had retention of urine. He gradually entered a uræmic state and died twelve days after the first pain.

Post-mortem Findings. The heart weighed 480 g. (normal 338±40) and showed some enlargement and a little dilatation of the right auricle and slight thickening of the wall of the left ventricle. The muscle wall was firm in consistency throughout and all the valves were normal. The aortic valve cusps showed fine congenital fenestration. A thin-walled aneurysmal sac, about the size of a golf ball, with a smooth lining and of 40-ml. capacity arose from the non-coronary sinus of Valsalva (Fig. 3A and B). In this

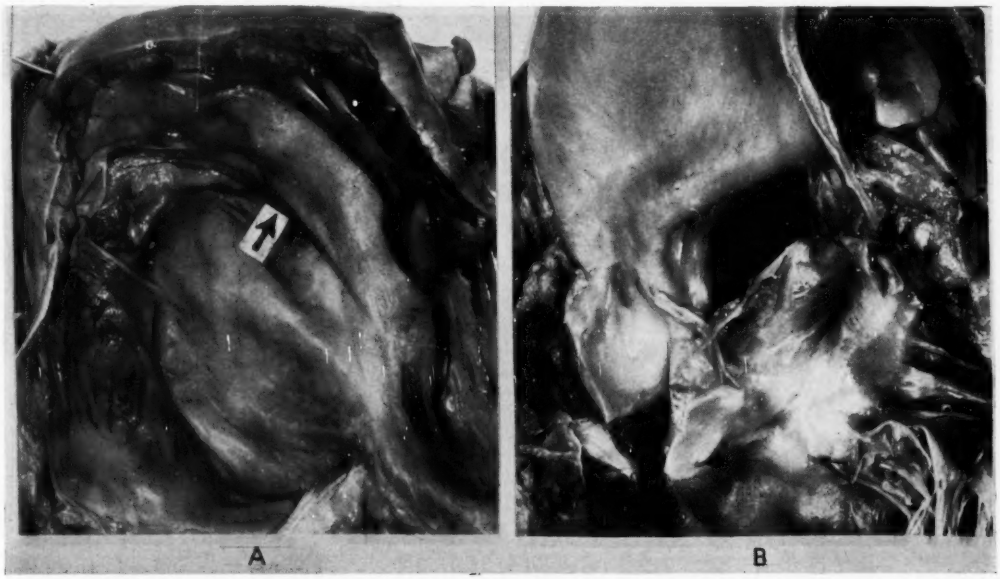


FIG. 3.—(A) The saccular aneurysm, about the size of a golf ball and involving most of the interauricular septum, can be seen protruding into the right auricle. The arrow marks the site of the small perforation. (B) The entrance to the aneurysm can be seen above the non-coronary cusp of the aortic valve. Case 2.

specimen the non-coronary sinus was situated posteriorly and the aneurysm bulged into the right auricle and had ruptured into that chamber through a tiny opening 2 mm. by 1 mm. in diameter in its extreme upper part near the roof of the auricle. As seen from the right auricle the aneurysm occupied practically the whole of the septal aspect. The fossa ovalis was obliterated but the posterior part of the limbus was distinguishable. The valve of the inferior vena cava ran onto the edge of the aneurysm and the distorted orifice of the coronary sinus could be seen at its lower margins.

Apart from signs of congestive heart failure, especially in the liver and lungs, no other naked eye abnormalities were present.

Histological sections of the aortic end of the aneurysm showed the uppermost part of the wall of the sinus of Valsalva to be composed mainly of fibrous tissue with occasional muscle fibres and irregular elastic lamellæ. Over two small stretches the wall was devoid of elastic tissue. There was no cellular infiltrate. Sections of the site of rupture showed no cellular reactions. The wall was composed of fibrous tissue with occasional muscle fibres and elastic lamellæ. A little thrombus was adherent to the ruptured edge. There was no histological evidence of syphilis. Apart from moderate venous congestion the only other histological findings were of moderate arteriosclerosis of the kidneys and confluent bronchopneumonia of the lower lobes of the lungs.

Clinical Picture

From a study of reported cases it is possible to describe a clinical picture that is often surprisingly constant. Excluding those cases that die immediately or within a few minutes, and these would appear to be uncommon (von Hauser, 1940; Ramsey and Mosquera, 1946; and Kawasaki and Benenson, 1946), the duration of life from the time of rupture is often considerable and has been recorded as from seven days (and this case died from cerebral hæmorrhage—Higgins, 1934) to seventeen years (Jones and Langley, 1949). From the onset of rupture until death is usually a matter of several weeks or months.

Aetiology. There is no doubt that the commonest cause of either a single or multiple aneurysm of one or more of the sinuses of Valsalva is a congenital defect, and this was present in 14 of the 23 cases recorded. Various possible embryological explanations have been put forward by Abbott (1919), Goehring (1920), and Venning (1951), and the most likely explanation would appear to be that these sinuses arise from defective development of the distal bulbar septum. As pointed out by Jones and Langley (1949), only two sinuses can be related to the distal bulbar septum embryologically, and it is not surprising therefore that these aneurysms are confined to the right coronary and non-coronary sinuses, and these authors state that there is no reported incidence of a congenital aneurysm arising from a left coronary sinus. However, there seems no doubt that the specimen described by Higgins (1934) which he considered to be congenital in origin did, in fact, arise from a left coronary sinus, but this is the only example we can find. Of the other causes subacute bacterial or ulcerative endocarditis leading to a mycotic aneurysm is the next most frequent (four cases). However, owing to the predilection of vegetations to form on any structural defect in the heart, their presence does not necessarily exclude a congenital origin to the aneurysm. If other congenital defects are also present such as a defect of the bulbar part of the interventricular septum, which is the commonest associated anomaly, being present in about half the cases according to Brown (1939), the congenital origin of the aneurysm is rendered likely even in the presence of infective damage. There were two such cases in the series—Venning's second case (1951) and that of Kawasaki and Schultz (1951). Only three of the aneurysms in the series were considered to be due to syphilis, although this is not infrequently stated as the commonest cause.

Anatomy. The most detailed study of the aortic sinuses and their anatomical relationships is that of Ostrum *et al.* (1938), but we do not hold with their contention that congenital aneurysms are rare and the most important ætiological factor is syphilis.

When one tries to correlate the position of the aneurysm with the site of rupture it is at once apparent that a wide variation in nomenclature exists and this difficulty has been pointed out by Jones and Langley (1949) and Raman and Menon (1949). There is no general agreement as to whether one of the coronary sinuses is anterior and the other two posterior, or whether two are anterior and one posterior. We think that this difficulty arises from the fact that each of the three sinuses subtends an angle of 120° and therefore rotation of the heart through only 60° will change the pattern of one sinus in front and two behind into that of one behind and two in front. Once the heart has been removed from the body, or even before that, it may be very difficult to be certain of the anatomical relationship of the sinuses one to another in the sagittal plane. Fortunately, this difficulty can be avoided if the sinuses are named according to the origin of the coronary arteries as suggested originally by Walmsley (1929). It is the most practical method and has the advantage of being independent of the rotation of the heart. The sinus from which the right coronary artery arises is called the right coronary sinus, the one from which the left coronary artery arises is named the left coronary sinus, and the one that does not give rise to a coronary artery is termed the non-coronary sinus. We have adopted this method and have applied it to the recorded cases.

At times more than one sinus of Valsalva is aneurysmal, as in the case of Micks (1940), or a single aneurysm may give rise to several daughter sinuses. Occasionally the rupture may lead into the left ventricle as well as the right, as in one of Eppinger's (1916) cases which showed multiple rupture.

Of the 23 cases that ruptured into the right side of the heart, one was still living so the exact site of the rupture remained unknown. Of the remaining 22 cases, the rupture into the right heart was single in 21, and in one case there were two ruptures, which makes 23 examples of rupture with autopsy verification. Of the 23, 14 had involved the right coronary sinus, 7 the non-coronary sinus, and only 2 the left coronary sinus. It will be seen, therefore, that the two sinuses nearest the right side of the heart anatomically are the most likely to give rise to aneurysms that rupture into it.

Age and Sex. There is a striking preponderance of men. Of the 23 cases that ruptured, 19 were men. This corresponds closely with Jones and Langley's (1949) figures for congenital aneurysms of the sinus of Valsalva, irrespective of rupture, in which 19 of 24 were men. The ages vary from 20 to 67, the average being 42 years. The syndrome never occurs in infants and young children, as even in the congenital cases the rupture does not occur until early adult life. Taussig (1947) states that the syphilitic ones commonly rupture later than congenital, but our figures do not support this—the three syphilitic cases ruptured at 27, 35, and 47, whereas the age at rupture of the congenital ones varied from 20 to 67.

Symptoms and Signs. From study of the reported cases it is apparent that not only are the symptoms and signs often characteristic in themselves, but in addition there is a diagnostic sequence of events. The syndrome usually begins with the sudden onset of severe pain in the chest or upper abdomen in a person who is apparently in excellent health. Although pain has not been mentioned by some authors (four cases) and in only three cases is there a statement to the effect that no pain was present, the majority did experience pain which closely simulates that of cardiac infarction. It usually occurs substernally and can at times involve the upper abdomen, but the characteristic radiation of cardiac pain to the neck, arms, jaw, or back is unusual, occurring in only three cases. Not uncommonly the pain appears to have been precipitated by effort, as in Hope's original patient who " on lifting a sack of flour felt a creak in the heart," in the patient of Eppinger (1916) who was climbing a mountain and bent to lift a heavy stone, in that of Kawasaki and Benenson (1946) who was swimming, and in our own patient who was straining at stool. Pain occurred in 16 of the series. It is usually severe and can be excruciating. It may last several hours but almost always, if the patient survives, it lessens and wears off and he then enters into an almost symptomless phase which we have termed the latent period. The cause of the pain is not clear, and although it presumably arises from interference with the coronary circulation it is difficult to see how this occurs when the aneurysm involves the non-coronary sinus. Of the seven examples where only the non-coronary sinus was involved, six experienced severe pain and in one pain is not mentioned. Cardiac infarction is not associated with the rupture, although one case has been recorded by Chipps (1941) in which the aneurysm, although it did not rupture, arose from the left coronary sinus, compressed the left coronary artery, and thereby caused cardiac infarction.

At the time of the pain a murmur appears in the chest, and although this may alter in character and other murmurs may appear, it is sufficiently characteristic to render the diagnosis highly likely. It is usually loud, harsh, and superficial in character and is accompanied by a coarse thrill. As a rule it is best heard near the centre of the sternum or a little to the left of it in the second, third, or fourth intercostal spaces. It characteristically occupies both phases of the cardiac cycle, either as a to-and-fro or a continuous noise, and the accentuation may be on systole or diastole. It is commonly described as sawing, whirring, or machinery in type, and not only has it been likened to the murmur of a patent ductus arteriosus but has actually been operated on in that mistaken belief (Wood, 1950). Such a murmur throughout systole and diastole was present in no fewer than 21 of the 23 cases. Probably the main cause of the systolic element is a flow of blood through the ruptured orifice of the aneurysm. Possibly in those cases with an associated ventricular septal defect this defect also contributes to the systolic murmur. In other cases the systolic element may be added to by a concomitant distortion of the aortic or tricuspid valves. The diastolic murmur is due either to the flow of blood through the perforation of the aneurysm or to aortic valve incompetence as a result of interference with one or more cusps adjacent to the aneurysm.

The phase in the history that we have called the latent period, during which the pain wears off and the patient may become well enough to leave his bed or even return to work, as did both our patients, was clearly recognizable in 17 cases, and in 12 of these its duration could be estimated with reasonable accuracy and varied from as little as three days (Herrmann and Schofield, 1947) to as long as 17 years (Jones and Langley, 1949), the usual period being a few weeks.

During or towards the end of this latent period the patient notices increasing dyspnœa; this is followed, usually rather rapidly once dyspnœa sets in, by signs of failure of the right side of the heart (17 cases). It has been emphasized by some authors that the absence of cyanosis is striking and characteristic, and this is attributed to the shunt being from the left to the right side of the heart. We feel that this is of little value in diagnosis. Cyanosis may, in fact, be early when it is due to shock, as in our Case 1, or later when the rise in venous pressure associated with right-sided failure supervenes: the cyanosis may then be extreme and specially commented on as in the case of Laederich and Poumeau-Delille (1928).

At about the time of onset of the right-sided heart failure, two sets of signs appear which, in combination, are themselves suggestive of the diagnosis; namely, those resembling aortic incompetence and those of tricuspid incompetence, the aortic being more commonly present.

A collapsing pulse, capillary pulsation, or a wide pulse pressure recorded on the sphygmomanometer was present in 21 of the 23 cases. There is no doubt that often wide pulse pressure is due directly to incompetence of the aortic valve, one or more cusps of which becomes deformed as a result of the juxtaposed aneurysm, but at times the aortic valve cusps are healthy and in these cases the peripheral signs are presumably the result of the arteriovenous shunt, and then the diastolic element of the continuous murmur presumably arises at the site of the rupture of the aneurysm and not at the aortic valve. The peripheral pulse is often strikingly collapsing and in our Case 1 we were reminded of the description by James Hope (1839) who found the pulse of Thurnam's patient to be " singularly jerking, especially in the carotids. I have never felt a pulse equally jerking. It was like a hard ball, forcibly shot through the vessel."

Systolic pulsation of the liver or the cervical veins was mentioned in ten cases. Herrmann and Schofield (1947) maintain that engorgement of neck veins with systolic pulsation of them and of the liver are more common when the aneurysm ruptures into the superior vena cava or right auricle than into the right ventricle. Our figures support this in that of the ten cases in which such pulsation was specifically mentioned seven had ruptured into the right auricle alone, one opened into the right auricle and right ventricle, one into the right ventricle, and one into both the right and left ventricles.

Perhaps not surprisingly the tendency in these patients is for deterioration to be remorseless, and although autopsy specimens do occasionally show signs of healing at the site of the rupture we can find no examples of spontaneous closure of the orifice. However, really sudden death appears to be surprisingly uncommon, as mentioned previously. The duration of life from the time of rupture in the series varied from seven days (Higgins, 1934; Herrmann and Schofield, 1947) to 17 years (Jones and Langley, 1949), but it is more commonly a few weeks or months. The cause of death is usually congestive heart failure (13 cases) and in two cases it was due to subacute bacterial endocarditis. One died from cerebral hæmorrhage. A surprising finding was that five cases clearly died from uræmia, the blood urea in this series varying from 105 to 345 mg. per 100 ml. The cause of this is not apparent and histological examination of the kidneys in our two cases did not reveal any satisfactory explanation. It is most unusual to find this degree of fatal uræmia as a result of right ventricular failure, particularly when there is no gross disease of the kidneys.

Investigations

Although the commonest investigation that has been undertaken is the electrocardiogram, it is obvious that the one most likely to prove of help would be cardiac catheterization if the patient's condition warranted it.

The electrocardiogram was recorded in 17 cases and in only one was it commented on as normal (Venning's second case, 1951). It is, however, commonly abnormal in the absence of rupture also, and complete heart block has been recorded in such a patient by Duras (1944) presumably from pressure of the aneurysmal sac on the bundle of His. The effect on the auricle was seen in that auricular fibrillation was present in four cases, auricular tachycardia in two, and auricular extrasystoles in one. Nodal interference was shown by one example of A-V nodal rhythm and two of A-V block. The effect on the ventricle caused five to show right axis deviation and one right bundle branch block.

It has been claimed by several authors (Hirschboeck, 1942; Herson and Symons, 1946; Arias and Baudino, 1952) that the presence of right axis deviation associated with suspected aortic incompetence is of diagnostic value, especially if it develops while the patient is under observation, as happened in Herrmann and Schofield's second case, but there is no doubt that the diagnosis can be made when no axis deviation (Macleod, 1944) or even left axis deviation (Eppinger, 1916; Jones and Langley, 1949) is present, and we feel that the electrocardiographic findings are so inconstant that they give little assistance to diagnosis.

As far as we can ascertain, only two cases have been catheterized, that of Arias and Baudino (1952) and our Case 1. Arias and Baudino give only a few details of the catheter findings and their patient was alive at the time of publication, so that an autopsy confirmation of the diagnosis is not available: their case is further complicated by the fact that they suspected also the presence of a persistent left superior vena cava.

It is clear that blood from the aorta, if it enters the right auricle or ventricle, will cause an increase in the oxygen content and pressure on that side, and the condition is essentially that of an arteriovenous aneurysm. Taussig (1947) is of the opinion that the main flow of blood from the aneurysm into the right heart occurs during diastole and that it is this rather than incompetence of the aortic valve which causes the wide pulse pressure.

Although of no value as far as diagnosis of rupture is concerned, radiology of the heart may sometimes reveal spherical or glove-finger like shadows on either border of the heart, which have been interpreted in life as aneurysms of the sinus of Valsalva and confirmed at autopsy by Albrecht (1936). However, aneurysms that project from the outline of the heart are unlikely to rupture into it. Venning (1951) has drawn attention to a fluoroscopic sign that he found in one case, namely, expansile pulsation visible in the smaller branches of the pulmonary artery. This, together with a collapsing pulse, suggests a fistula between the aorta and lesser circulation. However, presumably the same sign would also be found even more pronounced in rupture of an aortic aneurysm into the pulmonary artery, which is actually a commoner syndrome than the one we are describing.

Differential Diagnosis

On occasion, the presence of an unruptured aneurysm of the sinus of Valsalva can simulate the syndrome in so far as some pain in the chest and a loud to-and-fro murmur may be present, as in the case of Snyder and Hunter (1934) and Case 5 of Ostrum *et al.* (1938); but the typical sudden onset of symptoms in an apparently healthy subject is absent, no interference with the tricuspid valve has been recorded, and the patient does not go into heart failure.

The syndrome most closely resembling that of rupture of an aneurysm of the sinus of Valsalva into the right side of the heart is that of rupture of an aortic aneurysm into the pulmonary artery, and even long survival is consistent with that diagnosis (White *et al.*, 1941). This subject has been admirably reviewed by Nicholson (1943). In both conditions severe præcordial pain, followed by the development of dyspnœa and then congestive heart failure, with a machinery murmur and signs of aortic incompetence can occur. But the points that distinguish rupture of an aortic aneurysm into the pulmonary artery from perforation of an aneurysm of a sinus of Valsalva into the right heart are that in rupture of a sinus of Valsalva hæmoptysis is not common, while in the aortic aneurysm cases hæmoptysis is common, no tricuspid incompetence occurs (Porter, 1942), and, of

course, clinically and more often radiologically, the presence of the aortic aneurysm is detectable

The sudden pain in the chest, often precipitated by exertion and followed by aortic incompetence, is suggestive of rupture of an aortic valve cusp, either healthy or diseased, as Hope himself thought, but here the murmur is diastolic and is soon accompanied by left ventricular failure and there is no accompanying tricuspid incompetence.

A patent ductus arteriosus may present a diagnostic problem as the murmur can be strikingly similar, although it is usually best heard rather higher. The absence of a sudden catastrophe and of pain are strong points against the diagnosis. Wood (1950) investigated a case that was mistaken for a patent ductus and at operation it was found that a mycotic aneurysm of a sinus of Valsalva had ruptured into the pulmonary artery.

Another condition that may simulate rupture of a sinus of Valsalva into the right heart is spontaneous rupture of the interventricular septum in myocardial infarction. Sudden cardiac pain followed by gross right-sided heart failure with cardiographic evidence of right-sided dilatation or right bundle branch block may be present (Philip, 1954), but the fact that the murmur and thrill are systolic only (Wood, 1944) and that the electrocardiogram reveals cardiac infarction should prevent a mistake, although again these patients may live for a surprising length of time, the longest recorded being four years ten months by Wood and Livezey (1942). Similarly, as pointed out by Smith (1950) in his review of rupture of a papillary muscle of the heart, the profound shock and aggravation of cardiac pain is accompanied by the appearance of a harsh murmur which is apical and confined to systole, and the cause in over half these cases is again cardiac infarction. However, rupture of one of the mitral chordæ tendinæ is characterized by a harsh murmur in both systole and diastole, and this is usually antedated by bacterial endocarditis, but there is no evidence of arteriovenous communication.

Treatment

Surgical correction should prove feasible because of the characteristic clinical picture with the possibility of confirmation by cardiac catheterization, the fact that these patients often live for several weeks or months after rupture, the latent period that may follow the rupture during which the patient's general condition remains reasonably good, the fact that the rupture is commonly single and the orifice usually small, and the possibility of keeping the right heart relatively bloodless by using the heart–lung machine. Unfortunately, our case where this was attempted did not survive the operation. The only other example where surgical cure was attempted is that quoted by Burchell (1954) in which Kirklin (unpublished) unsuccessfully attempted to close a rupture of a non-coronary sinus through a right auricular approach. Burchell states that aneurysms of the right coronary sinus (right anterior) rupture into the right ventricle, whereas those of the non-coronary (posterior) rupture into the right auricle. He thinks, therefore, that rupture of the sinus from the non-coronary cusp should prove more easy to deal with surgically because it can be attacked either from the atrial or aortic side and its origin would not be associated with the origin of the coronary artery. Our figures regarding rupture of the non-coronary sinuses support these views, in that all 7 ruptured into the right auricle, but of the 13 examples of rupture of a right coronary sinus aneurysm only seven ruptured into the right venticle alone, four ruptured into the right auricle alone, and one into both right ventricle and right auricle (our Case 1) and one into both ventricles (Eppinger, 1916).

Summary

From study of our two cases and of 21 other examples of rupture of the sinus of Valsalva into the right side of the heart, it is possible to construct a clinical syndrome that should be recognized at the bedside with reasonable confidence. If the patient's condition is well enough the diagnosis can be confirmed by cardiac catheterization, and detailed findings are given of one such case.

In addition to the physical signs themselves, it is the characteristic train of events that supports the diagnosis. The patient is usually male and apparently previously well without heart disease.

At the time of the rupture he is usually seized with severe pain in the chest or upper abdomen, and on auscultation a characteristic loud continuous murmur is heard near the centre of the sternum or to the left of it, often accompanied by a thrill. After a few days the pain is apt to wear off and he may become deceptively well and even return to active life for a time. We have used the term latent period to draw attention to this phase. Gradually, however, he becomes dyspnœic and this increases until finally right-sided heart failure supervenes. At, or before, this final stage gross signs of an unusual combination of lesions are present, namely those of aortic and tricuspid incompetence, and a strikingly wide pulse pressure, associated with systolic expansion of the cervical veins and liver. Death results from congestive heart failure as a rule or from subacute bacterial endocarditis, but some cases die with uræmia and the reason for this is unknown. The commonest cause of aneurysm formation and of rupture is a congenital defect of the distal bulbar septum.

James Hope has never received due credit for his accurate clinical description of Thurnam's case and of his logical deductions from the findings post mortem. It is fitting to quote here from an elegy pasted in the third edition of his book in the library of the Royal College of Physicians of London.

> " He opened wide the portals of the heart
> And bad us hearken to its varied beat,
> Taught us the rules of stethoscopic art
> And shewed disease, slow mining, in its seat."

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THE DIAGNOSIS OF TRICUSPID STENOSIS

BY

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The clinical features of tricuspid stenosis have never been clearly defined. The diagnosis has usually been made in the late stages of the disease or it has only been revealed at necropsy. According to Friedberg (1949), the signs of tricuspid stenosis include accentuation of the *a* wave of the jugular pulse in normal rhythm, a diastolic or presystolic murmur at the left sternal edge, and enlargement of the right atrium radiologically; and tricuspid valve disease is suggested by a pulsating liver and a positive systolic venous pulse in a patient with systemic venous congestion, cyanosis, ascites, and valvular heart disease. White (1951) considers that the tricuspid diastolic murmur is difficult to distinguish from the murmur of mitral stenosis transmitted from the apex, and describes enlargement of the right atrium with a prominent systolic jugular pulse, in the absence of irreversible tricuspid ring dilatation as corroborative signs of tricuspid stenosis. Bramwell and King (1942) emphasized the powerful presystolic wave in the jugular pulse and the tall P wave in the electrocardiogram in cases of tricuspid stenosis. Kossman (1955) has drawn attention to the tricuspid opening snap. Reviews of necropsy material show that the diagnosis is made in only 10 to 15 per cent of cases (Cooke and White, 1941; Smith and Levine, 1942). Ferrer *et al.* (1953) state that the clinical diagnosis of tricuspid stenosis is unsatisfactory and is possible only in advanced cases.

Although rheumatic tricuspid stenosis is rare and its clinical features are usually over-shadowed by those of the concomitant mitral valve lesion, it is our belief that the diagnosis is important for the following reasons: it may masquerade as heart failure; it always modifies the clinical features of mitral stenosis and accounts for certain signs that, if attributed to the mitral lesion, would give a false impression of the physiological situation; and rarely it is the dominant lesion and may be severe enough to warrant valvotomy.

The purpose of this paper is to clarify the criteria upon which a confident diagnosis of tricuspid stenosis can be made during life, both at the bedside and by means of certain routine investigations, and whether the lesion is mild or advanced. It is based on a study of fifteen cases, and constitutes an elaboration and extension of the criteria outlined by one of us previously (Wood, 1954).

MATERIAL

There were fourteen cases of rheumatic mitral stenosis with tricuspid stenosis, nine of them occurring in a consecutive series of three hundred cases of mitral valve disease studied in detail by Wood (1954), an incidence of 3 per cent. Although tricuspid stenosis modified the clinical features of the associated mitral valve disease in all cases, it was the dominant lesion in only three. Six cases had trivalvular disease, there being an additional aortic lesion in five and pulmonary stenosis in one.

A single case of isolated tricuspid stenosis in a patient with presumed disseminated lupus erythematosus will be described separately.

Clinical Features of the Rheumatic Cases

Age and Sex. There were twelve women and two men, their ages ranging from 20 to 48 and averaging 36 years.

Antecedent Rheumatic Infection. There was a previous history of rheumatic fever in eight cases and of chorea in two.

Symptoms. The average age at the onset of symptoms was 31 years. Effort intolerance was considerable in six cases, moderate in six, and slight in two. Orthopnœa and paroxysmal cardiac dyspnœa occurred in only three instances, and both pulmonary apoplexy and congestive hæmoptysis, as defined elsewhere (Wood, 1954), were conspicuous by their absence.

The first symptom in two cases of dominant tricuspid stenosis was fluttering in the neck, especially on effort, due to the early development of giant *a* waves; in one case it preceded other symptoms by ten years.

Levine and Thompson (1937) emphasized that the ability to lead a fairly active life despite recurrent œdema and ascites was characteristic of tricuspid stenosis, and Smith and Levine (1942) found that the average duration of life under these circumstances was 7·5 years. Three of the more advanced cases in this series behaved in this manner.

Jugular Venous Pressure and Pulse. Presystolic pulsation in the jugular pulse in tricuspid stenosis was described by Mackenzie (1902). All eight cases with normal rhythm in this series showed a giant *a* wave in the jugular pulse ranging from 4 to 10 cm. above the sternal angle (Fig. 1); this giant *a* wave provided excellent evidence of tricuspid stenosis when there were no other signs of an extreme pulmonary vascular resistance. In these eight cases *v* was insignificant except in one instance complicated by congestive heart failure secondary to mitral stenosis with pulmonary hypertension.

In five of the six cases with auricular fibrillation, the venous pressure ranged between 6 and 10 cm. above the sternal angle and the venous pulse was systolic. This high venous pressure proved good evidence of tricuspid stenosis provided three conditions were fulfilled; namely, that the ventricular rate was controlled, that there were no other signs of a high pulmonary vascular resistance, and that the mitral valve was stenosed rather than incompetent.

The form of the venous pulse in tricuspid stenosis is characteristic even when there is auricular fibrillation and no giant *a* wave, for the *y* descent is usually too gentle to admit of any other diagnosis. When the venous pressure is high in other conditions, the downstroke of *v* (*y* descent) is

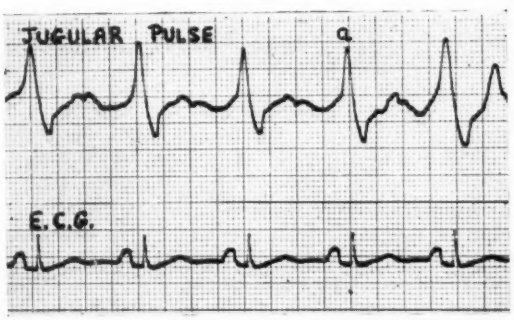

FIG. 1.—Jugular phlebogram from a case of tricuspid stenosis with normal rhythm, showing giant *a* waves.

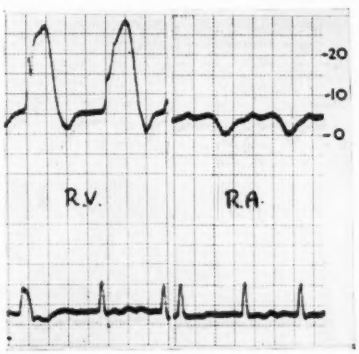

FIG. 2.—Right atrial and right ventricular pressure pulses from a case of constrictive pericarditis, showing a steep *y* descent, dominant *y* trough, and rapid equalization of diastolic pressures.

steep, right atrial and right ventricular diastolic pressures equalizing with the opening of the tricuspid valve at the summit of *v*, and falling together to the trough *y*, which is the lowest pressure reached by the relaxing right ventricle (Fig. 2). Following *y* right atrial and right ventricular diastolic pressures rise sharply together, as further filling is resisted by the distended right ventricle so that a conspicuous *y* trough is formed. In constrictive pericarditis the ascent following *y* is especially sharp, because the rigid pericardium prevents further filling relatively early in diastole; the situation is similar in tense pericardial effusion, and not very different in advanced heart failure with or without tricuspid incompetence when the right ventricle is overloaded. In tricuspid stenosis, however, right atrial and right ventricular diastolic pressures do not equalize at the summit of *v* when the tricuspid valve opens, the obstruction causing a pressure gradient across the valve as the ventricular pressure falls in early diastole. The right atrial pressure declines more gradually, and since the right ventricle offers no resistance to filling, there is no sharp ascent from the *y* nadir; indeed, right atrial and right ventricular diastolic pressures may not equalize at all in severe cases. The whole effect on the venous pulse is to produce a relatively gentle *y* descent with little or no rebound which can be recognized at the bedside (Fig. 3). This observation alone led to a clinical diagnosis of tricuspid stenosis in several of our cases. The same kind of pressure pulse may be recorded from the left atrium in cases of mitral stenosis (Owen and Wood, 1955).

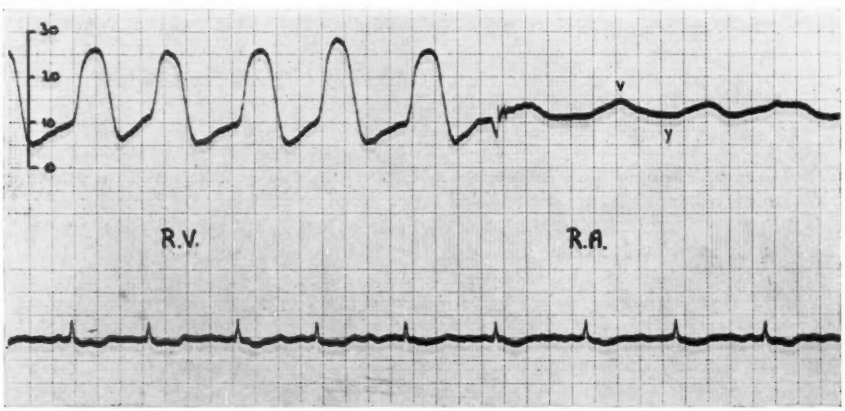

FIG. 3.—Right atrial and ventricular pressure pulses from a case of tricuspid stenosis with auricular fibrillation, showing a gentle *y* descent, insignificant *y* trough, and slow equalization of diastolic pressures.

Pulse. Normal rhythm was present in eight cases and auricular fibrillation in six. The pulse was small and firm in nine cases, water-hammer in quality in the three with aortic incompetence, and anacrotic in the two with aortic stenosis.

Colour. Peripheral cyanosis was observed in nine cases, presumably due to vasoconstriction associated with a low cardiac output. Neither jaundice nor excessive pigmentation was noticeable.

Cardiac Impulse. The characteristic palpatory sign of tricuspid stenosis was absence of the right ventricular heave usually felt in cases of mitral stenosis with a high pulmonary vascular resistance. The absence of this sign is, of course, in harmony with uncomplicated mitral stenosis, but in such cases, the venous pressure is normal.

Heart Sounds and Murmurs. On deep inspiration accentuation of the first heart sound and of the opening snap at the tricuspid area was observed in two of the three cases with dominant tricuspid stenosis.

A presystolic or diastolic murmur, waxing on inspiration, was heard over the tricuspid area in

all but one case (Fig. 4). Although this physical sign has long been recognized (Duroziez, 1868), it may easily be overlooked unless due care is taken. A tricuspid systolic murmur, also maximal on inspiration, was heard in only four instances, and was attributed to associated tricuspid incompetence. Auscultatory signs of mitral valve disease (stenosis in all but one) were always present in addition.

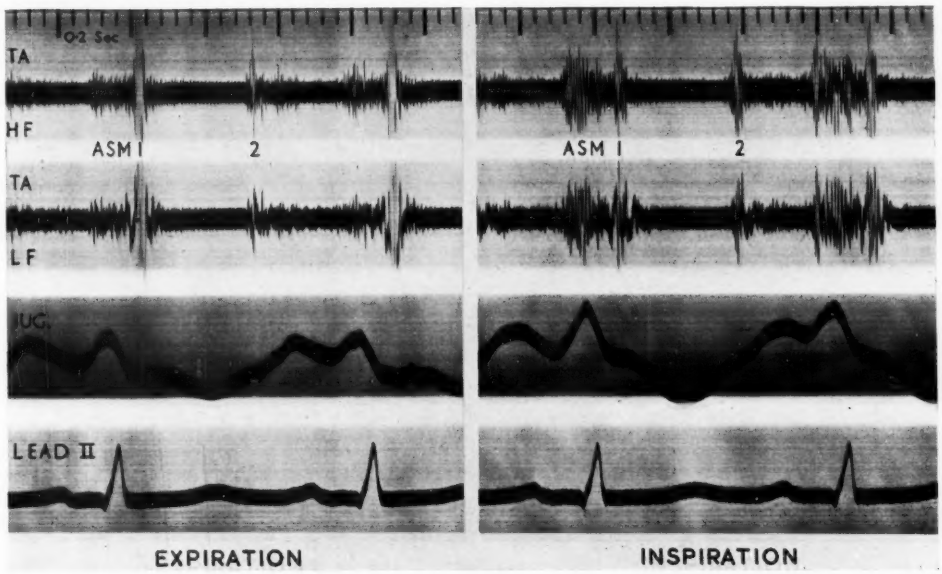

FIG. 4.—Phonocardiogram from the tricuspid area in a case of tricuspid stenosis, showing waxing of the presystolic murmur (ASM) on inspiration. Both records were taken with the same degree of amplification.

The Electrocardiogram. The characteristic feature of the electrocardiogram was a tall right atrial P wave, measuring more than 2·5 mm. in height, in the absence of electrocardiographic evidence of considerable right ventricular hypertrophy (Fig. 5), and as such it was observed in seven of the eight cases with normal rhythm, the mean height of the P wave being 3·7 mm.; the exception was the mildest case in the series. Unlike the pure P pulmonale, the P wave of tricuspid stenosis is nearly always widened owing to delay in its left atrial component due to concomitant mitral stenosis.

Electrocardiographic evidence of moderate right ventricular hypertrophy was present in three cases, two of which had a moderately raised pulmonary vascular resistance and one pulmonary stenosis. Left ventricular hypertrophy was found in four cases, all of which had aortic valve disease.

RADIOLOGY

Dressler and Fischer (1929) emphasized that enlargement of the heart to the right in the absence of pulmonary venous congestion was strong evidence of tricuspid stenosis. The most characteristic feature in our series was conspicuous dilatation of the right atrium without enlargement of the pulmonary artery (Fig. 6), this combination being observed in 11 out of the 14 cases; of the 3 exceptions two had enlargement of the pulmonary artery due to coincident pulmonary hypertension secondary to mitral stenosis, and one had pulmonary valve stenosis with post-stenotic dilatation of the pulmonary artery. Pulmonary venous congestion was absent or slight in ten, the tricuspid

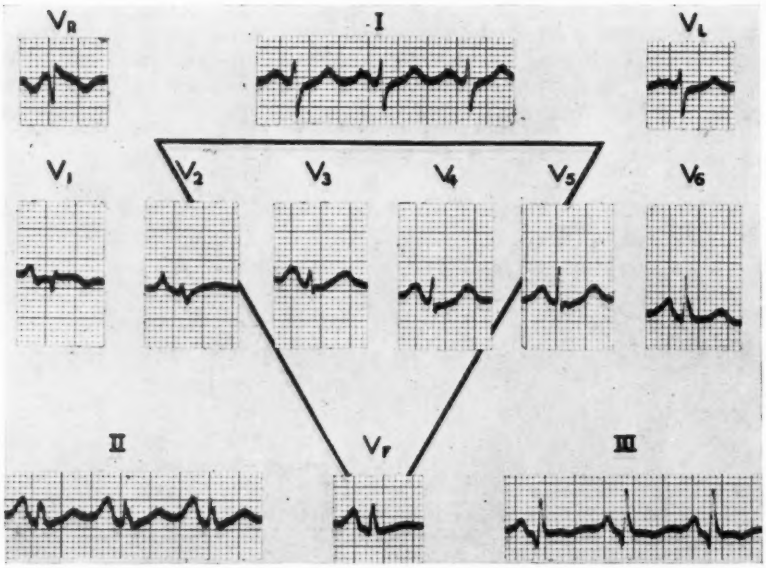

FIG. 5.—Electrocardiogram from a case of tricuspid stenosis with normal rhythm, showing tall right atrial P waves and no evidence of right ventricular hypertrophy.

stenosis tending to lower the cardiac output; but it was considerable in four cases with severe mitral stenosis requiring surgical relief. Dilatation of the left atrium was moderate in 11 and slight in 3 cases. A prolonged search for calcification of the tricuspid valve was fruitless in all instances.

ISOLATED TRICUSPID STENOSIS

A case of disseminated lupus erythematosus with isolated tricuspid stenosis is included in this series, because as far as we are aware, this is the first time such a lesion has been recognized clinically. Of 23 fatal cases described by Baehr *et al.* (1935), a non-rheumatic verrucous endocarditis of the mitral or tricuspid valve was observed in thirteen. Gross (1940) found obvious macroscopic involvement of the tricuspid valve in 6 of his 23 cases. Bagenstoss (1952) states that an abacterial verrucous endocarditis occurs in 40 per cent of all cases and that it is found with equal frequency on both sides of the heart. In their series of 34 cases Shearn and Pirofsky (1952) observed an apical diastolic murmur in four; in two of these necropsy was performed and revealed Libman-Sachs endocarditis of the mitral valve in each case.

Case Report. A man, aged 33, previously in good health, had been ill for one year with irregular fever, effort dyspnœa, and recurrent hæmoptyses. A systolic murmur was heard at the left sternal edge, but there was no anæmia, petechiæ, nor systemic emboli; the sputum was negative for tubercle bacilli, repeated blood cultures were sterile, and he did not improve following prolonged antibiotic therapy. Serial skiagrams showed right atrial dilatation, slight cardiac enlargement, transient lung shadows, and persistent enlargement of a right hilar gland (Fig. 7). On examination, his general condition was quite good, but he had a low-grade fever and sinus tachycardia; the venous pressure was raised and showed *a* and *v* waves of equal amplitude 5 cm. above the sternal angle at 45°; at the left sternal edge there was a presystolic murmur and an early systolic murmur, clearly maximal on inspiration. The erythrocyte sedimentation rate (Westergren) was 17 mm. in one hour, and there was a polymorphonuclear leucocytosis, but no LE cells in the peripheral blood. The electrocardiogram was normal. On cardiac catheterization an 8-mm. Hg. diastolic pressure gradient across the tricuspid valve was demonstrated and the indirect left atrial pressure was normal. There was subjective improvement following prolonged steroid therapy, and the skiagram showed a diminution

in the size of the right hilar gland as well as disappearance of the right apical lesion, but the heart murmurs and the venous pressure and pulse remained unchanged.

In this case, there was no clinical nor physiological evidence of any other valve lesion and a diagnosis of subacute disseminated lupus erythematosus with isolated tricuspid stenosis was made.

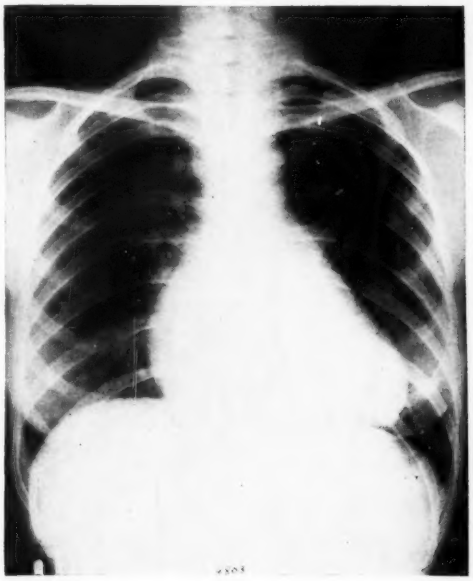

FIG. 6.—Skiagram showing dilatation of the right atrium without enlargement of the pulmonary artery and without pulmonary venous congestion in a case of dominant tricuspid stenosis.

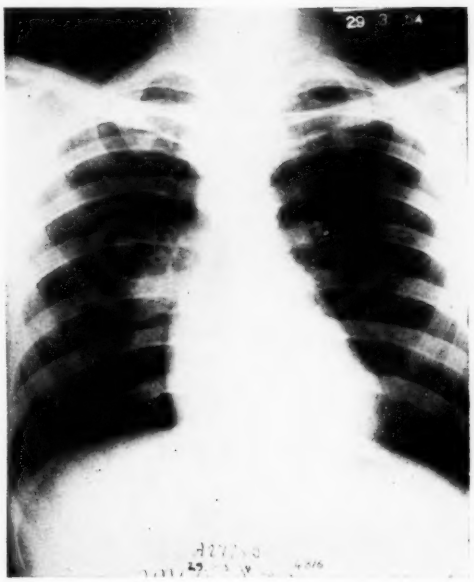

FIG. 7.—Skiagram from a case of isolated tricuspid stenosis, probably due to disseminated lupus erythematosus, showing enlargement of right hilar glands and slight right atrial dilatation.

CATHETER STUDIES

A diastolic pressure gradient across the tricuspid valve has been described by Gorlin and Gorlin (1951) and by Ferrer *et al.* (1953). Twelve of the fifteen cases in this series were investigated by means of cardiac catheterization and the results are shown in the Table. Pressures were recorded with a Sanborn electromanometer and polyviso, using the sternal angle as reference point. Oxygen consumption was measured with a Sanborn metabulator and blood gas analysis on the Van Slyke apparatus.

In each case the diagnosis was proved by the demonstration of a diastolic or presystolic pressure gradient, averaging 6 mm. Hg, across the tricuspid valve. This is best seen when the intracardiac pressure is recorded continuously as the catheter is withdrawn from the right ventricle to the right atrium; normally right atrial and ventricular diastolic pressures are identical (Fig. 8). The gradient has been measured as the greatest difference between right atrial and ventricular pressures during ventricular diastole. With normal rhythm the maximum gradient is presystolic (Fig. 9) and with auricular fibrillation it is early diastolic (Fig. 10).

The pulmonary vascular resistance was normal in all but two cases in which it was moderately increased. It was measured as mean P.A.P. *minus* mean L.A.P. (indirect) *divided by* Cardiac output (litres a minute). The cardiac output was less than 4 litres/min. in eight cases. In three instances there was considerable elevation of the left atrial pressure due to mitral stenosis which required mitral valvotomy.

TABLE I
RESULTS OF CATHETER STUDIES

Case	*Valve lesions* (in order of clinical dominance)	Pressures in mm. Hg								Arterial oxygen saturation (percentage)	Cardiac output (l./min.)	Pulmonary vascular resistance (units)
		Tricuspid diastolic gradient	Right atrium				Right ventricle	Pulmonary artery	Left atrium (indirect)			
			a	*x*	*v*	*y*						
1	MS. TS.	5			10	5	24/0	24/8	10/6	92	2·6	2
2	MS. TS.	4			7	4	25/0	25/10	10/7	92‡	4	2
3	PS. TS. MS.	5	5	−1	1		65/0	26/13	4	94	6·8	2
4	MS. AS. TS.	3			4	1	24/−2	24/15	10/8	93	3·4	3
5	MS. TS. AI.	6	5	−2	0	−1	20/−1	20/12	12/7	95	3·8	1
6	MS. TS. AI.	3	3	−2	0		25/0	25/10	16/9	94	4·7	1
7	AS. TS. MI.	3			10	2	28/−1	28/5	8/2	91	2·7	2
8	Isolated TS.*	8	10	4	10	4	20/2	20/7	5/1	95	4·8	1·7
9	MS. TS.†	8			8	3	65/−5	65/30	35/20	90	3·7	5·5
10	MS. TS.†	6	6	1	2		40/0	40/20	24/12	92	3·6	2
11	MS. TS.†	13	13	6	14	7	55/0	55/35	23/20	90	2·9	7
12	TS. MS. Tricuspid valvotomy	8			4	1	15/−7	15/5	4	96	3·3	1

* Case 8 had disseminated lupus erythematosus. † These patients have had mitral valvotomy. ‡ = assumed. TS = Tricuspid stenosis. MS = Mitral stenosis. AS = Aortic stenosis. AI = Aortic incompetence. PS = Pulmonary stenosis.

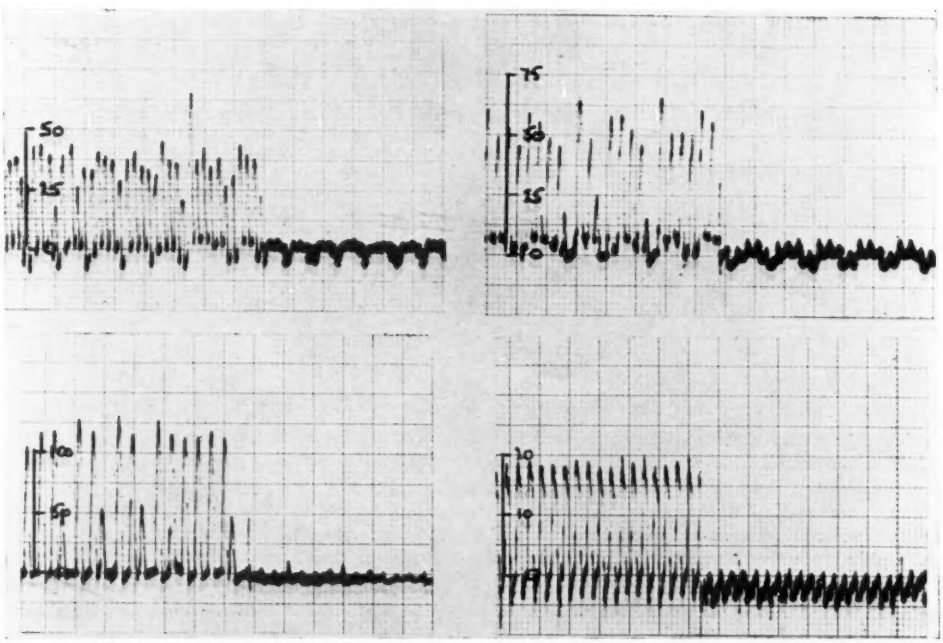

FIG. 8.—Pressure tracings during withdrawal of the catheter from right ventricle to right atrium in four cases of uncomplicated mitral stenosis showing that right atrial and ventricular diastolic pressures are normally identical.

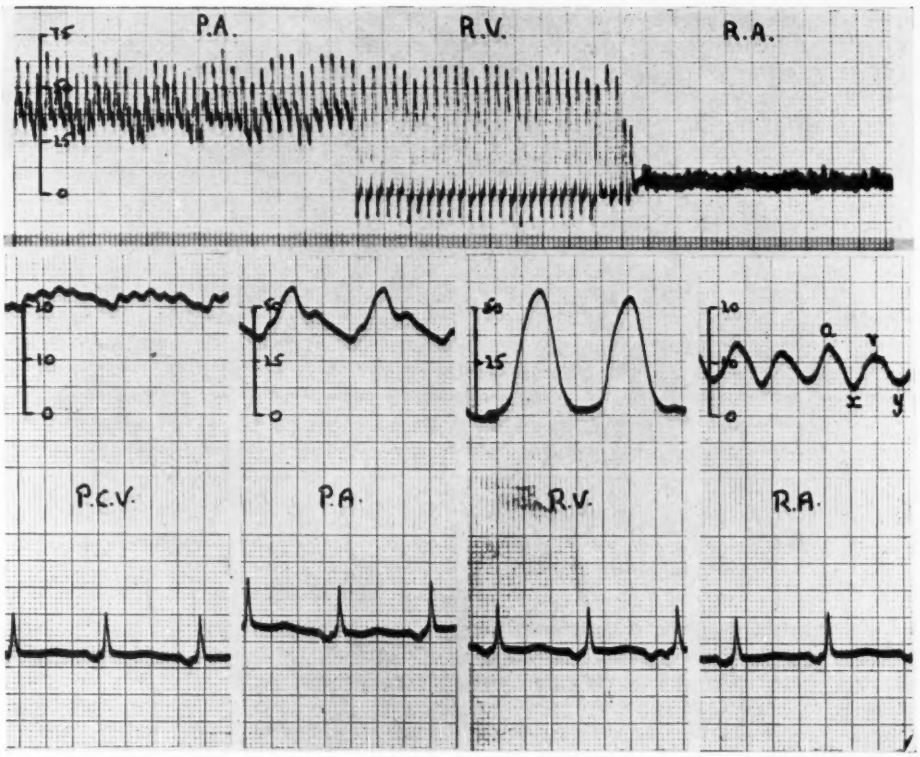

FIG. 9.—Right atrial and right ventricular pressure pulses and withdrawal tracing from a case of tricupid stenosis with normal rhythm, showing a 9 mm. Hg presystolic pressure gradient across the tricuspid valve.

In one case with dominant tricuspid stenosis, the most severe in the series, tricuspid valvotomy was performed by Sir Russell Brock. Pressures recorded before valvotomy demonstrated a diastolic pressure gradient across the tricuspid valve, a gentle *y* descent despite the high venous pressure, absence of a properly defined *y* trough, and very delayed equalization of right atrial and ventricular diastolic pressures. After valvotomy, right ventricular filling was obviously much more rapid, as indicated by the fairly steep *y* descent, clear *y* trough, and sharp rise in right ventricular diastolic pressure, resulting in virtual elimination of the diastolic pressure gradient at mid-diastole (Fig. 11).

DISCUSSION

A confident bedside diagnosis of tricuspid stenosis should not be difficult if the condition is borne in mind, and in fact was made in 80 per cent of this small series. Its 3 per cent frequency is based on a carefully analysed group of 300 cases of mitral valve disease, in 199 of which continuous intracardiac pressure tracings were obtained as the catheter was withdrawn from the right ventricle to the right atrium. Again, during the period in which we have been studying tricuspid stenosis, similar withdrawal tracings have been obtained in a total of 270 cases of mitral valve disease, of which only 11 had a diastolic pressure gradient across the tricuspid valve, giving a relative incidence of 4·1 per cent for tricuspid stenosis amongst all the mitral cases catheterized. The first figure is

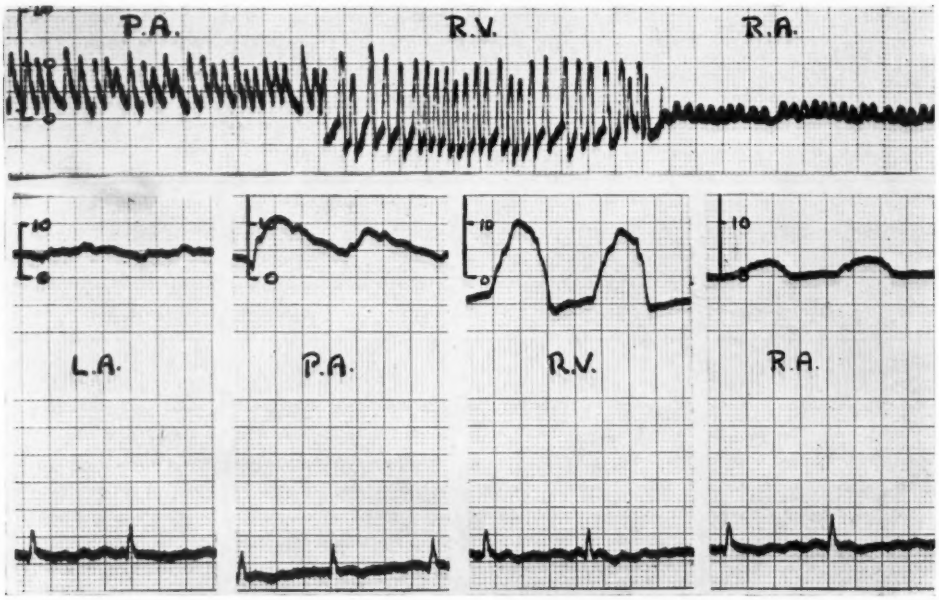

FIG. 10.—Right atrial and right ventricular pressure pulses and withdrawal tracing from a case of tricuspid stenosis with auricular fibrillation, showing a 5 mm. Hg diastolic pressure gradient across the tricuspid valve.

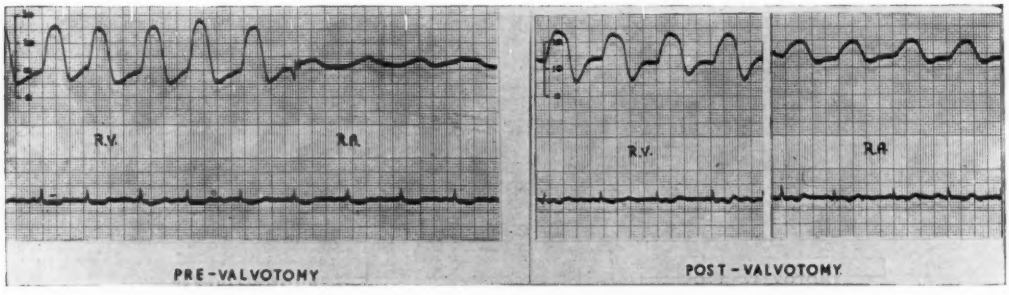

FIG. 11.—Right atrial and right ventricular pressure pulses in a case of tricuspid stenosis before and after tricuspid valvotomy, showing the change in the form of the *y* descent, the elimination of the diastolic pressure gradient across the tricuspid valve, and rapid filling of the right ventricle after valvotomy.

probably nearer the truth, however, because catheterization was more likely to have been carried out if tricuspid stenosis was suspected on clinical grounds.

In practice, the possibility of tricuspid stenosis should be considered in any case of mitral valve disease in which the jugular venous pressure is unquestionably raised. The differential diagnosis then lies between uncontrolled auricular fibrillation, severe mitral incompetence, a high pulmonary vascular resistance, pericardial effusion, and tricuspid stenosis, for in uncomplicated mitral stenosis the venous pressure is normal (Wood, 1954). If the rise in venous pressure is due to a rapid irregular ventricular rate, it soon subsides in response to digitalis therapy.

The raised venous pressure that may be associated with severe mitral incompetence is not yet fully understood, but it may be due primarily to left ventricular failure, leading to a diminished renal blood flow, sodium retention, and hydræmia; or it may be due to a filling defect of the right ventricle from the bulged interventricular septum (Bernheim effect). We have never encountered tricuspid stenosis in the presence of severe mitral incompetence, so if the latter is present there is little point in looking further for the cause of the raised venous pressure.

If a high pulmonary vascular resistance is responsible for the abnormal jugular venous pressure pulse, there is likely to be a giant *a* wave with normal rhythm or a steep *y* descent and conspicuous *y* trough with auricular fibrillation; while the latter combination at once excludes tricuspid stenosis, the former, of course, does not. The chief clinical features of severe pulmonary hypertension are a heaving right ventricle, damped mitral auscultatory signs, loud pulmonary valve closure or functional pulmonary incompetence, strong right ventricular preponderance electrocardiographically, and considerable dilatation of the pulmonary artery radiologically. When any of these features are present, tricuspid stenosis can only be diagnosed at the bedside if there is an unequivocal inspiratory tricuspid presystolic or diastolic murmur. A separate tricuspid opening snap, accentuated during inspiration, may be heard occasionally, but is usually unconvincing unless the mitral valve is heavily calcified when its tricuspid origin may be assumed with confidence. Unfortunately, only one of the fifteen cases of tricuspid stenosis in this series had *calcific* mitral stenosis, so we have little information to offer concerning isolated tricuspid snaps. The exception had trivalvular disease and was too complicated to be helpful.

The differential diagnosis between tricuspid stenosis and pericardial effusion may sometimes be difficult, for in both conditions there is a high venous pressure and apparent dilatation of the right atrium without evidence of advanced pulmonary hypertension. However, the jugular pulse has no specially characteristic feature in pericardial effusion, *a* and *v* waves being of more or less equal amplitude in cases with normal rhythm, and the *y* descent being in harmony with the height of *v* in cases with auricular fibrillation. If necessary, the presence or absence of pericardial effusion can be proved during cardiac catheterization by demonstrating whether or not the heart shadow lies beyond the right atrial border as defined by the tip of a suitably looped catheter (Wood, 1950).

Isolated tricuspid stenosis of rheumatic origin has not been described, although Clements (1935) reported a case as such despite clear necropsy signs of associated mitral valve disease. In the case of isolated tricuspid stenosis in our series, probably due to Libman-Sachs endocarditis, the clinical features of the tricuspid lesion itself were identical with those of the rheumatic cases.

Summary

A series of fourteen cases of rheumatic tricuspid stenosis is presented. The lesion was found in 3 to 4 per cent of all cases of mitral valve disease, but was overshadowed by the latter in all but three instances.

A case of probable disseminated lupus erythematosus with isolated tricuspid stenosis is also reported.

The clinical features of tricuspid stenosis are described and include the following.

(1) Absence of symptoms of pulmonary venous congestion: chronic œdema and ascites are only seen in advanced cases.

(2) A high venous pressure in the absence of a high pulmonary vascular resistance, pericardial effusion, uncontrolled auricular fibrillation, or severe mitral incompetence.

(3) A venous pulse showing a giant *a* wave in cases with normal rhythm, and a gentle *y* descent without a properly defined *y* trough in those with auricular fibrillation.

(4) A quiet right ventricle and unimpressive pulmonary second sound.

(5) A diastolic or presystolic murmur at the tricuspid area, waxing on inspiration.

(6) An opening snap at the left sternal edge in the presence of *calcific* mitral stenosis.

(7) A tall right atrial P wave in the absence of electrocardiographic evidence of right ventricular hypertrophy.

(8) Conspicuous dilatation of the right atrium without enlargement of the pulmonary artery, and with relatively little pulmonary venous congestion.

The diagnosis was proved in twelve cases during cardiac catheterization by demonstrating a presystolic or diastolic pressure gradient across the tricuspid valve, averaging 6 mm. Hg.

Of the fifteen cases, twelve were diagnosed initially at the bedside by means of these criteria, and three were discovered during cardiac catheterization.

We should like to thank the cardiological technicians at the Brompton Hospital and the National Heart Hospital, particularly Mrs. Milne and Mr. Brabrook-Norman, for their invaluable help. We are also indebted to Mr. D. F. Kemp of the Photographic Department, the Institute of Diseases of the Chest, for the illustrations.

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CASE REPORTS

CARDIAC INVOLVEMENT IN LYMPHOSARCOMA WITH SPONTANEOUS RUPTURE OF THE HEART

BY

E. C. B. KEAT AND V. R. TWYMAN

From the Putney Hospital, London

Secondary neoplastic involvement of the heart is not infrequent in routine necropsies of patients dying of malignant disease but cardiac failure as a presenting feature remains uncommon, the cause of the failure often not being diagnosed till necropsy. The importance of its recognition during life, particularly in patients suffering from the reticuloses, is that the failure may benefit from radiotherapy, whereas treatment on conventional lines is often disappointing. The following case is of interest, in that cardiac failure and a lump in the abdomen were the two presenting features, and after three weeks of intractable failure, sudden death occurred from rupture of the heart.

A woman of seventy-six was admitted to Putney Hospital in congestive failure. Her story was that she had complained to her doctor of abdominal discomfort and constipation, and a lump was felt in the left iliac fossa. Further questioning revealed, however, that she had been short of breath for two to three months, with swelling of the ankles and abdomen for ten days, and orthopnœa for five days. There was no paroxysmal nocturnal dyspnœa, but cough had been present for some weeks. On examination, she was orthopnœic with a tinge of cyanosis in the lips and showed uncontrolled auricular fibrillation and signs of congestive heart failure, with a small left pleural effusion. The heart was grossly enlarged, the apex beat being in the anterior axillary line, the impulse weak. There was a presystolic gallop rhythm at the apex and a soft blowing diastolic murmur of aortic incompetence to the left of the sternum. In the abdomen, there was a smooth rounded swelling in the left iliac fossa which from rectal and bimanual examination appeared to be situated in the uterus. The bowels were constipated but flatus passed normally, the urine contained a trace of albumen. Chest X-ray confirmed considerable enlargement of the heart with widening of the mediastinum, a left plural effusion, and possibly a small pericardial effusion. The electrocardiogram showed normal voltage with a digitalis effect. After a period of slow progress with digitalis and neptal, she died suddenly twenty-three days after admission, having conversed normally five minutes before death.

Necropsy by one of us (V.T.) showed the body of a well-covered elderly woman with œdema of the legs and sacrum. The heart was grossly enlarged with extensive involvement by growth of all coats, as shown in Fig. 1 and 2. The pericardium contained a fair quantity of recent blood and there was a small tear through the myocardium, 1 cm. below and lateral to the left posterior aortic cusp. The pericardium was thickened by growth and adherent in places and the myocardium considerably replaced by similar tumours which in parts extended on to the endocardial surface as can be seen in the figure. This feature was particularly marked in the right atrium and there were also small nodular masses on the endocardial surface of the ventricles below the attachment of the atrio-ventricular valves. Histologically, the myocardium and pericardium showed extensive direct infiltration by lymposarcoma. In addition, there appeared to be spontaneous rupture with hæmorrhage through the myocardium involved by lymphosarcoma. There were also a considerable number of enlarged glands in the mediastinum, the average size being 12–25 mm. in diameter. In the abdomen, the uterus was found to be enlarged to twice its normal size, with a rounded neoplastic mass in the body. Histologically the uterus shows a metastatic deposit of lymphosarcoma in the endometrium. The lymph gland shows lymphosarcoma.

Bisel *et al.* (1953) found cardiac metastases in as many as 21 per cent of 500 consecutive autopsies on patients who had died of neoplastic disease, though they included cases of leukæmia in the series, the incidence being highest in those with leukæmia and malignant melanoma, followed by carcinoma of the breast and of the lung and lymphoma, the pericardium being the main site in approximately half the cases.

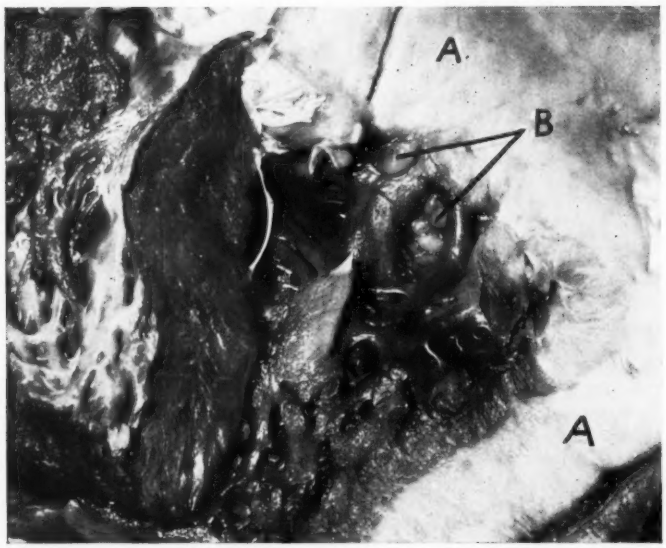

FIG. 1.—Interior of the right ventricle, showing extension of growth from the right auricle and extensive involvement of myocardium (A). Small nodules on the endocardium are seen at (B).

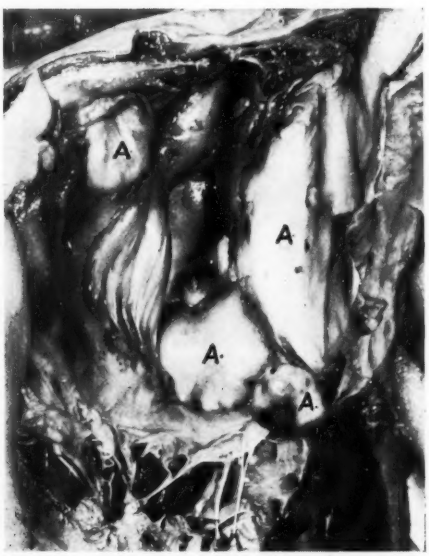

FIG. 2.—Interior of right atrium, showing invasion by growth (A).

Nabarro (1953) has recently reviewed involvement of the heart by malignant lymphoma and has shown that when cardiac signs present, intractable congestive failure with considerable cardiac enlargement and gallop rhythm is a frequent method of presentation. In the present case, these features are shown, as well as hypotension which is common in recorded cases, and auricular fibrillation which has been noted on previous occasions. This latter may be paroxysmal or persistent and it is suggested that this sometimes improves on radiotherapy (Garvin, 1941). Sudden death by cardiac rupture is, however, rare. We have been able to find only two further cases of rupture of the heart from secondary deposits, the first from a primary in duodenum, (McNamara *et al.*, 1937) and the second from melanotic sarcoma. Spontaneous rupture by itself is often reported, and is generally the result of coronary artery disease with thrombosis or hæmorrhage, but rupture has been recorded in the past from gummata, tuberculosis, and hydatid disease and associated with a tumour in the cerebellum (Patin, 1935).

Summary

In this case cardiac failure was followed by rupture of the heart due to neoplastic involvement by lymphosarcoma. Neoplastic disease of the heart should be considered when patients known to suffer from the reticuloses or neoplastic disease develop cardiac failure or when there is unexplained cardiac failure.

We wish to record our thanks to Dr. Warner for allowing us to publish this case, to Dr. F. A. Knott, visiting pathologist to Putney Hospital for the section reports, and to Miss Turnbull, Charing Cross Hospital photographic department for the photographs.

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EXTRASYSTOLES ARISING FROM THE MAIN BUNDLE OF HIS

BY
EVAN FLETCHER
From the Belfast City Hospital

Extrasystoles arising from a homogenetic focus in the main bundle of His are very rare. Lewis (1911) and Lewis and Allen (1913) each published a single case, and laid down the criteria for the cardiographic diagnosis. They stressed the importance of the marked similarity of the ectopic beats to the ventricular complexes of the sinu-auricular beats. The P waves related in time to the ectopic beats may immediately precede their ventricular complexes with a shortened P–R interval, or more often, they follow their ventricular complexes and are seen between the QRS and T waves of the ectopic beats. There is no disturbance of the sequence of the P waves by the extrasystoles. Holzmann (1951) published an example of this rare rhythm in which some of the ectopic beats were interpolated. Scherf and Boyd (1950) have recorded a unique case of ventricular parasystole in which the independent automatic centre of impulse formation was situated in the main bundle. Another example is the case of Scherf and Schott (1953), but this record is complicated by intra-ventricular block.

Case History

A man, aged 22 years, was referred to hospital on account of irregularity of the heart beat. He had no cardiac symptoms, and on clinical examination there was no abnormality of the heart apart from the extra-systolic arrhythmia. Serial cardiograms confirmed that the P waves in all leads related in time to the ectopic beats resembled the P waves of the supra-ventricular beats. Cuttings from lead II are shown in Fig. 1.

Cardiographic Analysis

The ectopic beats in A, B, and C closely resemble the ventricular complexes of the sinu-auricular beats. Their R waves are slightly higher, but this minor degree of aberration is much less than in the case described by Lewis and Allen (1913), and does not invalidate the placing of the ectopic centre above the bifurcation. Moreover, the intra-ventricular conduction time of the ectopic beats is the same as that of the normal beats (0·07 sec.). As the T waves are isoelectric, the similarity of the P waves related in time to the ectopic beats to the P waves of the sinu-auricular beats is made more obvious. The second P wave of B, and the fifth P wave of C are slightly distorted by the positive T waves of the extrasystolic beats. The second P wave of C precedes the QRS of the extrasystole with a shortened P–R interval. This is similar to Fig. 1 of Lewis' case (1911). When the P wave following an extrasystole is blocked, the post-extrasystolic interval is compensatory (sixth P wave of A and second P wave of C). The auricular cycle lengths of A and B are 0·98, 0·94, 0·92, 0·90, 0·90, 0·96, 0·92, 0·92, 0·92, 0·96 sec., the range of variation being small, within 0·08 sec. The auricular cycle lengths of C are 0·76, 0·78, 0·84, 0·96, 0·92 sec., the range of variation being 0·2 sec., i.e. greater than A and B. The auricular cycle lengths of D are 1·12, 1·20, 1·06, 1·24 sec. The extrasystoles in D are more aberrant than in A, B, and C, but they are produced here as close inspection of their ventricular complexes shows evidence of small superimposed negative P waves indicating retrograde auricular activation by the ectopic beats.

In addition to the extrasystoles, there is first degree A-V block (P–R 0·22–0·26 sec.), the delay in A-V conduction being greater in the post-extrasystolic beats (P–R 0·25–0·28 sec.), due to fatigue of the conducting pathways by the two preceding ventricular beats occurring close together. The T waves of the post-extrasystolic beats are more negative than those of the other supra-ventricular beats.

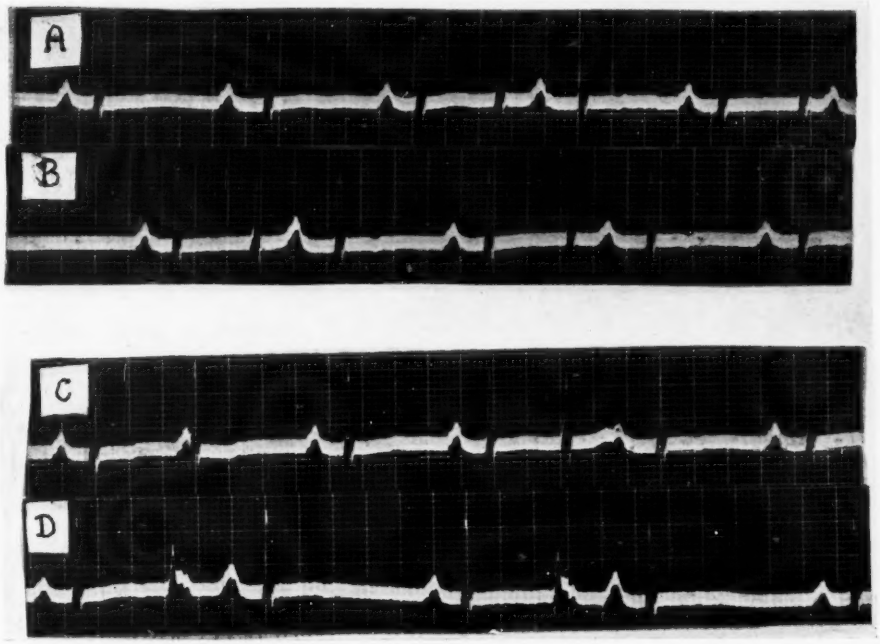

FIG. 1.—Extrasystoles arising from main bundle of His. Lead II. A and B are continuous records, C and D are separate. Time markings: 0·04 sec.

Discussion

The fact that the extrasystoles are interpolated confirms that their focus of origin is in the ventricles, for interpolated auricular extrasystoles have not been conclusively proven to occur in the human heart (Scherf and Schott, 1953). The essentially normal pattern of ventricular activation during the propagation of the ectopic beats indicates that their site of origin is above the bifurcation of the main bundle of His, either in the main stem or in the A-V node. Since nodal extrasystoles activate the auricles in a retrograde fashion, the excitation wave discharges the sinus pacemaker, thereby causing a shift of the dominant rhythm. There is no shift of the sinus pace maker in this case by any such mechanism, even though D shows evidence of retrograde conduction of the ectopic beats along the conducting pathways in the auricles. Presumably therefore the ectopic centre is situated in the main bundle rather than in the A-V node itself. Alternatively, it could be assumed that the ectopic centre is in the A-V node, and that the sinus pace maker is protectively blocked against A-V impulses. Such blocked nodal extrasystoles, as in Wenckebach and Winterberg's case (1927), could not be differentiated from main stem extrasystoles. There is no evidence in A and B that the time sequence of the P waves is influenced by the ectopic beats, the narrow range of variation of the auricular cycle lengths noted above being presumably spontaneous. In D, however, the auricular cycle length immediately following each extrasystole is longer than the immediately preceding auricular cycle length. The explanation appears to be that the double auricular activation by the retrograde conduction of the ectopic beat and the rapidly succeeding sinus beat, leads to fatigue of the conducting pathways in the auricles, so that when the next sinus beat occurs, activation of the auricles is slightly delayed and the auricular cycle length is thereby prolonged. It is apparent therefore that if extrasystoles arising in the main bundle are conducted backwards to

the auricles, they may influence the sinus rhythm even though they do not discharge the sinus pace maker. In such a case, the strict criteria laid down by Lewis (1911) and Lewis and Allen (1913) for the diagnosis of stem extrasystoles, concerning the " absence of disturbance of the sequence of the P waves," may require revision.

Summary

A case of extrasystolic arrhythmia is analysed, in which the ectopic centre appears to be situated above the bifurcation of the main bundle of His. The difficulty of locating the focus, either in the main stem or A-V node, is discussed. Attention is drawn to the possible effect of retrograde conduction on the sequence of the sinu-auricular beats, apart from discharge of the sinus node, with particular reference to auricular fatigue. The great rarity of this disturbance of rhythm is noted, and reference made to the few previously reported instances.

I wish to acknowledge the helpful advice of Dr. David Scherf, New York Medical College.

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CONGENITAL CORONARY ARTERIO-VENOUS ANEURYSM

BY

P. H. DAVISON, B. H. McCRACKEN, AND D. J. S. McILVEEN

From the General Hospital, Birmingham and Hill Top Hospital, Bromsgrove, Worcs.

Congenital arterio-venous aneurysms are not rare and it is, perhaps, surprising that they do not occur more frequently for the development of the vascular bed is extraordinarily complex. They are most commonly situated in the brain, limbs, or lungs, and the local and general disturbances of function that they produce are now well known. Involvement of the coronary circulation must be most unusual for only three instances have been reported in the English journals (Halpert, 1930; Paul *et al.*, 1949). The following case is of interest because the arterio-venous aneurysm, which involved the circumflex branch of the left coronary artery, proved to be clinically indistinguishable from a patent ductus arteriosus, and the blood flow through it became so great that the patient died from congestive cardiac failure.

Case Report

Mrs. B.D., housewife of fifty-eight years, was admitted to the Birmingham General Hospital in February, 1954, with congestive cardiac failure. She had experienced bouts of palpitations for about ten years. In 1948 she was examined in a medical out-patient department when clinical and electrocardiographic examinations were normal and the symptoms were considered to be due to paroxysmal tachycardia. Subsequently she developed increasing dyspnœa on exertion, orthopnœa, and fatigue, and was admitted to another hospital in July, 1953. She was found to have congestive cardiac failure with auricular fibrillation. On repeated examinations a systolic murmur but no diastolic murmur was heard and the diagnosis made was rheumatic heart disease. She was re-admitted to the same hospital in November, 1953, again in cardiac failure, and during the course of this second admission, examinations by the same physician as before disclosed the development of a systolic and diastolic machinery type murmur in the pulmonary area. The cardiac failure responded to therapy but relapsed after she left hospital in spite of continued use of digitalis and mercurials and she was admitted to the General Hospital.

Previous Health. No rheumatic or other significant illness.

Family History. The patient was one of ten siblings of whom two died of " valvular heart disease " at the ages of eleven and fifty-four years respectively. Neither parent had known heart disease.

Clinical examination showed a rather thin woman in gross congestive failure with moderately severe dyspnœa, orthopnœa, and cyanosis. She was afebrile. The neck veins were distended and there was marked dependent œdema extending as high as the waist. There were râles at both lung bases and evidence of basal pleural effusions. The liver was enlarged 2·5–5 cm. below the right subcostal margin. The fingers were not clubbed. The pulse was completely irregular, of good volume and with a collapsing quality, and about 80 a minute. Blood pressure was 125/55. The heart was enlarged with a heaving apical impulse in the anterior axillary line, five inches from the midsternum in the sixth left interspace. There was a visible and palpable systolic lift of the præcordium to the left of the sternum and a systolic thrill was palpable in the second and third left interspaces close to the sternum. At the apex the first sound was followed by a loud harsh blowing systolic murmur (grade 3/6) well conducted into the axilla. At the base the pulmonic element of the second sound was accentuated and a loud murmur which extended through systole and diastole was audible over a wide area, being maximal in the pulmonary area.

Investigations. Red blood cells, 5·4 million; hæmoglobin, 106 per cent (Haldane); white blood cells, 8800; E.S.R., 1 mm. per hour (Westergren); Wassermann, negative; blood cultures, negative; serum chemistry —urea, 51 mg per cent; sodium, 130 m.eq./litre; potassium, 5·4 m.eq./litre; chloride, 97 m.eq./litre. X-ray films of chest showed generalized enlargement of the heart with pulmonary congestion and basal pleural effusions. The patient was too ill to fluoroscope. Electrocardiograms showed auricular fibrillation, right axis deviation, and neither right nor left ventricular preponderance. (The cardiogram in 1948 showed normal sinus rhythm and normal ventricular axis in standard limb leads.)

Hospital Course. The clinical diagnosis after admission was congestive cardiac failure due probably to patent ductus arteriosus. Treatment was aimed at improving the patient's condition enough to justify transferring her to the cardiac surgery unit at Hill Top Hospital. Digitalis, salt restriction, and œdema drainage by Southey's tubes did in fact produce a considerable improvement in the degree of cardiac failure, but two weeks after admission she developed a severe mental disorder with some classical features of a chronic schizophrenic reaction, negativism with resistance, at times violent, and periods of echopraxia and echolalia. No explanation for this occurrence was found in her serum chemistry, which was essentially the same as on admission, or in her previous mental history which had been impeccable. Periods of violence caused a relapse of cardiac failure and the outlook seemed serious enough to justify a trial of electroconvulsive therapy. A single treatment was followed after a few days by return to a fairly normal mentality. Her cardiac failure subsequently was relieved enough for her to be transferred to Hill Top Hospital seven weeks after admission. Cardiac catheterization was performed five days after her transfer in order to confirm the diagnosis of patent ductus before operation was undertaken.

Cardiac Catheterization. This was performed in the usual manner. Blood gas was analysed by the method of Van Slyke and Neill. Expired air was collected in a Tissot spirometer and analysed in a Sleigh general apparatus. The chambers of the right heart and the pulmonary artery were dilated. Attempts to enter a patent ductus were unsuccessful despite good catheter control. The findings, which are summarized in Table I, demonstrated a large left-to-right shunt into the right atrium, moderate pulmonary hypertension and high-output congestive heart failure.

TABLE I

CARDIAC CATHETERIZATION

Mrs. B. D., 58 years, 6/3/54. Height, 61 in.; weight, 119 lb.; surface area, 1·51 sq. m.

Pressures recorded in mm. Hg and measured from the sternal angle. Blood oxygen content expressed in volumes per 100 ml.

Site	Pressures		Blood samples	
	s/d	mean	O_2 content	% saturation
Left pulmonary artery	—	46	14·31	73
Right pulmonary artery	—	43	14·04	71·5
Main pulmonary artery	75/25	45	14·13	72
High right ventricle	76/14	—	14·42	73·5
Low right atrium	—	14	13·31	68
High right atrium	—	14	10·73	54·5
Left brachial artery	140/60	88	16·87	86

Oxygen capacity of blood: 19·66 vol./100 ml.
Resting oxygen consumption: 192 ml./min.
Resting cardiac output: 7·1 l./min.; 4·7 l./min./sq. m.
Effective systemic blood flow: 3·1 l./min.; 2·1 l./min./sq. m.
Left-to-right shunt: 3·9 l./min., equal to 56 per cent of total cardiac output.
The arterio-venous oxygen difference of the effective systemic blood flow was calculated from the high right atrial blood sample which probably approximates fairly closely to mixed venous blood.

In view of the unexpected results the operation was not undertaken. The patient's condition deteriorated steadily and she died four weeks after admission.

Necropsy. Apart from the heart the findings were not remarkable and consistent with severe, prolonged congestive heart failure. The heart weighed 490 g. and all chambers were dilated and hypertrophied. The ventricular and auricular septa were both intact and the foramen ovale closed. The mitral ring was dilated and the cusps a little thickened. The tricuspid ring was dilated and there was a plaque of thickened endocardium on the atrial aspect of the anterior cusp. The pulmonary valves were competent and the pulmonary artery dilated and thickened. The aortic valves were competent and normal apart from thickening of the left coronary cusp. The aorta showed minimal atheroma and the ligamentum arteriosum was firmly occluded. The right coronary artery was normal in origin, size and distribution and was free from atheroma. The left coronary aortic sinus was dilated, and the mouth of the left coronary artery so large that it was difficult to say where sinus ended and artery began. The left coronary artery was dilated and funnel-shaped. Its anterior descending branch arose normally, followed an orthodox course and was free from atheroma. The circumflex branch was thin-walled and grossly dilated throughout its entire length with an average diameter of 15 mm. (Fig. 1). It was greatly elongated and the dilated loops, coiled in serpentine fashion, were firmly adherent to each other and to the inferior aspect of the left atrial appendage

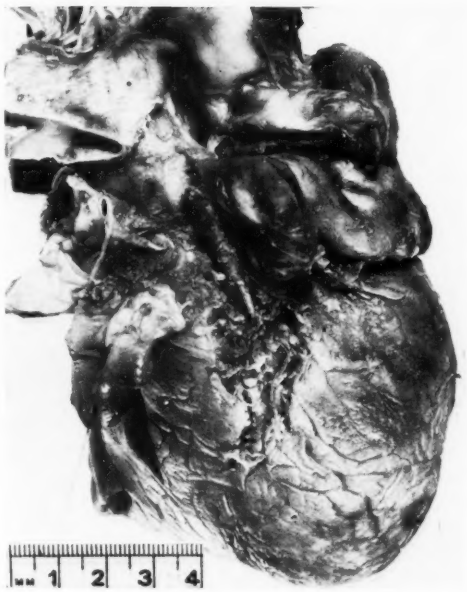

FIG. 1.—The heart from the antero-lateral aspect. The main pulmonary artery has been divided to expose the first part of the aorta, the left coronary artery and its branches. The dilated circumflex branch passes backwards beneath the left atrial appendage.

FIG. 2.—The heart from the postero-inferior aspect. The dilated circumflex artery is shown passing directly into the aneurysmal coronary sinus.

as they coursed backwards in the atrio-ventricular groove, overlying the great cardiac vein which was normal in size and position. The origins of the smaller branches of this dilated vessel, which normally supply the lateral and inferior aspects of the left ventricle, could not be demonstrated without destroying the specimen, but section through the lateral wall of the left ventricle showed branches of normal size. This dilated circumflex artery passed directly into the coronary sinus (Fig. 2). The latter was aneurysmally dilated and formed a thin-walled bag of blood 10 cm. in diameter on the postero-inferior aspect of the heart. The venous drainage into the coronary sinus appeared normal. Its anterior wall projected into the right atrium and the medial wall of the atrium in this area was so thin that it was accidentally torn at one point during dissection of the heart. The mouth of the coronary sinus was oval in shape and measured 8×5 mm. Its lips were thickened and rigid, projecting into the right atrium like the crater of a volcano. The jet of blood from this orifice impinging upon the anterior leaflet of the tricuspid valve was presumably responsible for the plaque of thickened endocardium observed there. Histological sections of the heart muscle taken from the lateral wall of the left ventricle showed no evidence of myocardial fibrosis; the capillaries and larger vessels were well filled with blood.

Discussion

The discovery of an arterio-venous aneurysmal communication between the circumflex branch of the left coronary artery and the coronary sinus at necropsy explained the anomalous clinical and physiological findings during life. In the absence of trauma and infective or degenerative changes in the vessel it is reasonable to conclude that the arterio-venous fistula was congenital in origin. Congenital arterio-venous aneurysms are known to increase gradually in size over the course of years and this necessitates a progressive rise in the cardiac output in order to maintain an adequate orthodox circulation in the presence of an increasing shunt. This hyperkinetic state may lead, ultimately, to congestive cardiac failure. In this patient the absence of any symptoms of coronary

insufficiency, the histological normality of the myocardium and the high-output congestive failure demonstrated by cardiac catheterization all indicate that death was directly attributable to the size of the shunt. This is not surprising for the aneurysm was taking approximately one-half of the total resting cardiac output.

In the previous reports of this anomaly (Halpert, 1930; Paul *et al.*, 1949) the right coronary artery was involved in two cases and probably a branch of the left coronary artery in the third. In Halpert's patient the condition gave rise to no symptoms or signs during life and was a necropsy finding in a man of 54 years who died from carcinoma of the stomach. In the first case described by Paul and his colleagues an arterio-venous aneurysm of the right coronary artery was discovered at exploratory thoracotomy in a boy of nine years with a continuous murmur in the fourth right interspace who had no disability and only slight cardiac enlargement. A full report is not available in their second case but the condition was again discovered at thoracotomy in a boy of 16 years who was thought to have a patent ductus arteriosus. At operation the murmur was found to arise from an abnormal bulge on the lateral wall of the left ventricle and this was attributed to an arterio-venous aneurysm of the coronary circulation.

A correct ante-mortem diagnosis was not made in the case reported here although this would have been possible from the data available. The clinical diagnosis of patency of the ductus arteriosus was firmy excluded by the findings at cardiac catheterization. The clinical and catheter findings were consistent with rupture of the right aortic sinus into the right atrium. In the elderly this condition is usually a complication of syphilitic or mycotic aneurysm of the aortic sinus. The absence of these infections and the competence of the aortic valve were against this diagnosis.

It would be difficult to make a confident diagnosis of coronary arterio-venous fistula during life without resort to exploratory thoracotomy. If the condition is suspected then direct sampling of coronary venous blood with a cardiac catheter should be attempted although the large venous outflow would make its introduction into the coronary sinus difficult. Normal coronary venous blood contains little oxygen and an oxygen saturation exceeding 30 per cent of capacity may be taken as evidence of an arterial shunt into the coronary circulation. This can arise from a coronary arterio-venous aneurysm or from anomalous pulmonary veins draining into the right atrium via a persistent left superior vena cava and the coronary sinus. General signs of systemic arterio-venous fistula should serve to distinguish the former condition. Retrograde aortic angiography might prove a simpler method of demonstrating the abnormal vessels.

Unfortunately such diagnostic perfectionism would bring no therapeutic reward for ligation of the abnormal vessel would carry a grave risk of death from myocardial ischæmia.

Summary

A 58-year-old woman presented with clinical features consistent with congestive cardiac failure secondary to a large patent ductus arteriosus. Cardiac catheterization demonstrated an arterial shunt into the right atrium. A congenital arterio-venous communication between the circumflex branch of the left coronary artery and the coronary sinus was discovered at necropsy.

We wish to thank Miss S. Segel for technical assistance and Mr. W. Dee for the photographs.

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PROCEEDINGS OF THE BRITISH CARDIAC SOCIETY

The THIRTY-FOURTH ANNUAL GENERAL MEETING of the British Cardiac Society was held at the Royal Infirmary, Manchester, on Thursday, May 26, 1955. The Chairman, CRIGHTON BRAMWELL, took the Chair at 9.30 a.m.; 126 members and 27 visitors were present.

PRIVATE BUSINESS

1. The minutes of the last Annual General Meeting, having been published in the Journal (**16**, 468, 1954) were taken as read and confirmed.

2. The balance-sheet for 1954–55 was presented, having been audited and found correct by A. Morgan Jones and E. Wyn Jones. The credit balance on May 9, 1955, was £1030 6*s*. 7*d*.

3. S. A. Levine was elected and acclaimed as an *Honorary Member* of the Society.

4. The following were elected *Extra-Ordinary Members*:
   Arnold Stott — G. E. S. Ward

5. The following Associate Members were elected as *Ordinary Members*:
   R. I. S. Bayliss — R. Hudson
   R. Byron Evans — P. Mounsey
   J. D. Hay — E. G. Wade
   B. B. Hosford

6. The following *Surgical Members* were elected:
   F. R. Edwards (Liverpool) — A. H. Siddons (London)

7. The following new *Associate Members* were elected and introduced to the President and the Chairman:
   D. W. Barritt (Bristol) — P. M. McAllen (London)
   R. S. Duff (London) — T. Semple (Glasgow)
   R. W. Emanuel (London) — T. B. Smiley (Belfast) (*Assoc. Surgical Member*)
   W. Lister (Plymouth) — R. Steiner (London)
   A. C. MacDonald (Glasgow) — R. S. Stevens (Worthing)
   I. K. R. MacMillan (London) — O. L. Wade (Birmingham)
   H. J. S. Matthew (Edinburgh)
   M. B. Matthews (Edinburgh)

8. C. G. Baker and A. R. Gilchrist were elected members of the Council in place of P. H. Wood and J. H. Wright (term of office expired).

9. It was agreed that Rule 1 of the Society should be altered to read:
   "The Society shall be called 'The British Cardiac Society'. Its objects shall be the advancement of knowledge of Diseases of the Heart and Circulation, and the promotion of good fellowship among those whose primary interest is in the practice of Cardiology, or in research in this or allied subjects."
   It was also agreed that Rule 4 of the Society should be altered to read:
   "There shall be a President of the Society who shall be nominated by the Council and elected by the Society. The Council shall give the Society at least one month's notice of the nomination, and if during that time any other nominations, which must be signed by ten Members, are received by the Council then the election shall be by ballot. He shall be elected for two years and may be eligible for re-election for further periods of one year to a total of five years on the recommendation of the Council. He shall be *ex officio* a member of the Council. He will represent the Society at home and abroad and may preside over meetings of the Council but not at the Scientific Meetings of the Society, for which a local Chairman will be elected annually."

10. The Secretary announced that the Council, at its previous meeting, had recommended that in future Associate Members should be allowed to attend the Private Business Session of Meetings of the Society,

provided it was decided that no good reason existed for their exclusion from any particular meeting, and the Secretary was instructed to circulate the Agenda of the Private Business to Associate Members in future.

Short Communications

A Classification of Systolic Murmurs

By Aubrey Leatham. Two varieties of systolic murmurs may be recognized, depending on their shape and relation to the heart sounds: (A) ejection murmurs, midsystolic and usually basal; and (B) regurgitant murmurs, pansystolic. Knowledge of their graphic configuration can be applied to clinical auscultation.

(A) Ejection systolic murmurs are midsystolic and are produced by turbulence from flow of blood through the aortic or pulmonary valves when there is stenosis, valvular damage without stenosis, dilatation of the vessel beyond the valve, or increased flow through the valve. There is an interval between the first sound and the onset of the murmur depending on the time taken by the ventricle to raise its pressure sufficiently to open the aortic or pulmonary valve. The flow and murmur begin as blood is ejected into the great vessels and rise to a crescendo about midsystole, diminishing as the ventricle relaxes and intra-ventricular pressure falls, and ceasing before the second sound produced by closure of the respective valve. Basal ejection vibrations can be recorded in many normal subjects and some slight increase in their intensity is probably responsible for most innocent murmurs.

(B) Regurgitant systolic murmurs are pansystolic and caused by flow of blood from a chamber or vessel that is at a higher pressure throughout systole than the receiving vessel or chamber. In mitral and tricuspid incompetence the ventricular pressure rapidly exceeds the atrial pressure and the backward flow and murmur begin very soon after the first sound. The flow and murmur continue right up to the second sound because the pressure difference between the two chambers is still great at the time of closure of the aortic and pulmonary valves, and tends to drown the second sound on clinical auscultation at the site of maximum intensity of the murmur. In some cases of mitral incompetence the murmur is maximal in late systole, but early systolic vibrations can always be recorded.

In ventricular septal defect with normal pressures the murmur is pansystolic because the left ventricular pressure is higher than the right throughout systole. In ventricular septal defect with high right-sided pressures and little left-to-right shunt, the pansystolic murmur is minimal or absent and there is an ejection midsystolic murmur from dilatation of the pulmonary artery. In patent ductus with normal pressures the left-to-right flow and murmur are continuous, and the murmur is obvious or maximal in late systole when an ejection systolic murmur would have diminished. With high pulmonary pressure and resistance and little or no left-to-right shunt the continuous murmur is replaced by a midsystolic ejection murmur from dilatation of the pulmonary artery. In two children with patent ductus and moderate elevation of pulmonary pressure and resistance but with obvious left-to-right shunt the pulmonary murmur was pansystolic presumably because the main left-to-right shunt was systolic.

In conclusion, it is hoped that the division of systolic murmurs into ejection midsystolic and regurgitant pansystolic murmurs will aid their indentification and classification.

The Clinical Syndromes of Patent Ductus with Pulmonary Hypertension

By R. M. Marquis and A. Rae Gilchrist. Twenty-six of a consecutive series of 252 patients with isolated patency of the ductus arteriosus did not conform to the typical pattern. Clinical recognition of the atypical case is usually possible, but the relative difficulty in diagnosis suggests that 10 per cent underestimates its incidence.

The 26 patients have three factors in common—absence of the continuous murmur, pulmonary hypertension, and the large size of ductus—but they form three distinct clinical groups that special investigations confirm.

Group I (8 cases, 2 operations, 3 autopsies). Pulmonary hypertension, secondary to large left-to-right shunt, sometimes sufficient to cause partial shunt reversal.

Group II (9 cases, 8 operations, 3 autopsies). Pulmonary hypertension, early in onset, initially sufficient to restrict the left-to-right shunt and probably advancing to shunt reversal.

Group III (9 cases, no operations, 2 autopsies). Pulmonary hypertension primary with permanent shunt reversal.

Peripheral cyanosis may be present in all groups. In the presence of shunt reversal central cyanosis may be generalized, dissociated, or only detectable on analysis of arterial blood distal to the ductus.

Some patients with continuous murmurs and large left-to-right shunts pass into Group I but Groups II and III never have continuous murmurs. In Group III pulmonary hypertension is the primary dysfunction and surgical occlusion of the ductus is probably unwise. Early surgery may be curative in Groups I and II.

Comparative Study of the Radiological Kinetics and the Arterial Blood Pressure in Congenital Heart Disease

By E. Donzelot, V. Serafini, J. Bougnoux, P. Kervoelen, and R. Heim de Balsac. To be published in full: *Brit. Heart J.*, **18**, January 1956.

The Intracardiac Electrogram as an Aid in Localization of Pulmonary Stenosis

By D. Emslie-Smith and K. G. Lowe (*introduced by I. G. W. Hill*). To be published in full: *Brit. Heart J.*, **18**, January 1956.

An Evaluation of Lead V4R in the Cardiographic Diagnosis of Right Ventricular Hypertrophy

By F. Camerini (*introduced*), J. F. Goodwin, and Max Zoob. To be published in full: *Brit. Heart J.*, **18**, January 1956.

The Postcommissurotomy Syndrome

By Cornelio Papp and M. M. Zion (*introduced*). In 22 of 105 patients (21%) who had mitral valvotomy, the immediate or late postoperative period was complicated by the postcommissurotomy syndrome (*P.C.S.*), The main symptoms were pyrexia, pericarditis, left pleural effusion, and a tendency to relapse. The *P.C.S.* has been atrtibuted to and confused with postoperative rheumatic activity because of pericardial involvement, pyrexia, the tendency to relapse, and the increased sedimention rate—common features to both. However, preceding streptococcal infection, joint swellings, myocardial and valvular involvement, and the effect of salicylate are the distinguishing signs of rheumatic disease and these are absent in the *P.C.S.* These two entities, therefore, should be clearly separated.

Pyrexia for a few days, left pleural effusion that absorbs within a fortnight, and fleeting signs of pericarditis are the accompanying signs of the early postoperative period in the uncomplicated cases. The *P.C.S.* is the accentuation, prolongation, and recurrence of these normal postoperative sequelæ rather than a superadded disease. The causes for persistence and relapse are local and not general. The effusion was found to be bloodstained in 9 out of 11 cases after the first week when in the controls without *P.C.S.* it was found to be serous. In addition, loculus formation was observed in four; aspiration of the loculi led to prompt recovery. Postoperative oozing from the auricular wound into the pleuro-pericardial space may be the main cause of the syndrome. Loculus formation and pulmonary consolidation beneath the effusion may represent added factors.

The *P.C.S.* has an invariably good prognosis—a feature also at variance with rheumatic fever—and has no adverse effect on the outcome of the operation.

The Ballistocardiogram and the Pulmonary Artery Pressure in Mitral Stenosis

By C. B. Henderson. The ballistocardiograms of 100 cases of mitral stenosis have consistently shown two abnormal waves. These waves are present in auricular fibrillation and in sinus rhythm and are named the RI and RJ waves. The RI wave is a footward deflection commencing 0·06–0·10 sec. after the Q wave of the electrocardiogram and the RJ wave is a headward deflection immediately following the RI wave.

The abnormality can be divided into five grades of severity. The grade varies with changes in pulmonary artery pressure as when the heart rate changes, and the duration of the preceding diastolic pause varies, with the changing phases of respiration, and with the improvement following successful mitral valvotomy. The higher the pulmonary artery pressure the higher is the grade of abnormality of the ballistocardiogram.

Evidence is presented chiefly in the form of ballistocardiograms and pressure tracings from the pulmonary artery recorded simultaneously to suggest that the abnormal waves are a result of right ventricular ejection. A close correlation is shown between the grade of abnormality of the ballistocardiogram and the pulmonary artery pressure in the 100 cases investigated. A prediction of the mean pulmonary artery pressure can be made in patients with mitral stenosis from the ballistocardiogram and in ten cases this was confirmed at subsequent catheterization.

The Quantitative Estimation of Valvular Regurgitation by Dye Dilution Curves

By Paul Korner (*introduced*) and John Shillingford. *Illustrated by a colour film.* In normal dye dilution curves the shape of the curve can be accurately predicted for any given cardiac output and volume between the site of injection and sampling point. The introduction of valvular incompetence causes a deviation from this normal pattern and the amount of this deviation is related to the amount of phasic regurgitant flow.

The validity of the hypothesis has been tested in a heart circulation model and found to have a high degree of accuracy. A standard nomogram has been calibrated from normal model curves and has been used for predicting the phasic regurgitant flow in the model.

A separate and independent nomogram has been calculated for man for the estimate of regurgitant flow This may be estimated either for the left or right sides of the heart at the time of cardiac catheterization by injecting the dye either into the pulmonary artery or into the right atrium.

Examples of the amount of phasic regurgitant flow in different valve lesions are shown and discussed.

The film shows the behaviour of the passage of dye through the heart model with and without valve incompetence and the application of the technique to man.

Observations on the History of the Pictorial Representation of the Heart

By A. Schott. The paper attempts to describe briefly some of the more important stages in the historical development of the pictorial representation of the heart. Starting with the Fasciculus Medicinæ of Johannes de Ketham of 1491, it includes references to Leonardo da Vinci, Vesalius, Eustachius, Fabricius, Lower, Haller, and Scarpa. The most recent is Quain as representative of the middle of last century. The paper is illustrated by slides.

Effects of Squatting

By E. P. Sharpey-Schafer. In normal subjects arterial mean and pulse pressure increased on squatting and there was vasodilatation of forearm vessels. Cases of heart failure showed no increase of pulse pressure or vasodilatation. On standing upright after squatting there was decrease of pulse pressure and constriction in normal subjects but not in cases of heart failure.

The results support the theory of baroceptor responses to acute pulse pressure changes.

Total and Peripheral Flow in Acute Myocardial Infarction

By G. de J. Lee (*introduced by E. P. Sharpey-Schafer.*) Eleven patients admitted to hospital with acute myocardial infarction were studied; two subsequently died as a result of their condition. Pulse rate, blood pressure, central venous pressure, cardiac output (Hamilton dye technique) and forearm bloodflow (venous occlusion plethysmography) were obtained. The observations were repeated after 4–6 weeks in those who recovered.

The central venous pressure was raised initially. Pulse rate varied between individuals, but tended to decrease with recovery. The initial pulse rate did not correlate well with the apparent severity of the infarct. Peripheral vasoconstriction, indicated by low forearm flow, was also most marked in the severe cases, and in some instances it was intense: this was sometimes associated with little fall in blood pressure.

Cardiac output in three cases without shock was normal in one and raised in two. In the remainder, the cardiac output was below normal and tended to be more reduced the severer the infarct. However, the cardiac output was not as low as in a separate group of patients with hypertensive cardiac failure. In the two patients who died from their infarcts, the cardiac output was 5·0 and 5·7 litres a minute respectively. Central blood volume was raised in all instances initially and returned to normal with recovery. This increase in central blood volume was less than in the group of patients with hypertensive heart failure.

Control of Quinidine Dosage by Blood and Urine Estimations

By D. Weitzman (*introduced by Graham Hayward*). Published in full: *Brit. Heart J.*, **17**, 534, 1955.

The Effects of Perfusion and Congestion of the Pulmonary Circulation on the Distensibility of the Rabbit's Lung

By Peter Harris (*introduced by Samuel Oram*). In these experiments the lungs of rabbits have been removed from the thorax and distended by positive pressure with air. Air has then been withdrawn from the lungs in small measured successive amounts and the intratracheal pressure recorded at each stage. In this way the relationship between pressure and volume in a distended lung can be determined and this relationship can be expressed in a graph. The curve that is derived is the static pressure-volume curve of the lungs, since the effects of viscous resistance to flow of air are eliminated and only the force of elastic recoil of the lungs is operating.

When the pulmonary circulation is perfused or congested in various ways, the static pressure-volume curve of the lungs is altered. An analysis of such curves leads to the following conclusions.

(1) The effects of perfusion or congestion of the pulmonary circulation on the static pressure-volume curve of the lungs are due entirely to alterations in the capillary circulation. The distension of arteries and veins has in itself no substantial mechanical influence on the lungs.

(2) Congestion of the pulmonary capillaries imposes a force on the lungs that tends to maintain them in a position of partial inflation.

(3) Congestion of the pulmonary capillaries also causes them to occupy a small measurable part of the alveolar air space.

The effects described may be applicable to the mechanical alteration of the lungs found in diseases of the mitral valve and in failure of the left ventricle.

Reactivity of Peripheral Blood Vessels to Adrenaline and Noradrenaline in Human Hypertension

By Robert S. Duff (*introduced by Geoffrey Bourne*). A method of measuring precisely, under controlled conditions, the purely local effects of minimal amounts of drugs on the calibre of blood vessels in the extremities is presented. Repeated determinations of the volume of blood flowing through portions of the limbs are made by venous occlusion plethysmography; at regular intervals solutions of drugs alternating with plain saline are introduced into the artery supplying the tissue during the course of a continuous, constant-rate, intra-arterial infusion.

Quantitative estimates of the peripheral vascular effects of very low concentrations of adrenaline and noradrenaline have been compared in various categories of patients with normal and raised blood pressure. A proportion of patients with raised blood pressure has been found to have increased sensitivity to one or both agents. Aetiological and therapeutic implications of this finding are discussed.

Electrocardiographic Changes in Experimental Hypothermia

By Gerald R. Graham (*introduced by W. Somerville*). Ventricular fibrillation is one of the main problems in artificial hypothermia for intracardiac surgery. Its incidence and mode of onset, under various circumstances, are still unsettled. Also, it is not clearly established whether warning signs, in the form of arrhythmias or electrocardiographic pattern changes, regularly occur before its onset.

To investigate these points, experiments were performed on anæsthetized dogs, maintained under artificial respiration but not otherwise operated on, that were cooled to 25° C. In one series, hypothermia was induced by extracorporeal circulation through a cooling coil; in the other, cooling was achieved by placing the dogs in an ice-bath. In both, the dogs were re-warmed over a period of a few hours. Intra-arterial blood pressure was recorded and continuous electrocardiographic control maintained (limb and chest leads), permanent records being taken at frequent intervals.

It was found that when ventricular fibrillation occurred it almost always did so without previous warning (arrhythmias or other electrocardiographic changes) that could not also be observed in other animals without the onset of ventricular fibrillation. QRS and S–T–T changes were principally related to the cooling effects *per se* and were reversible. These abnormalities seemed less marked with bath cooling. Typical cardiographic changes and their reversibility were presented and their significance discussed.

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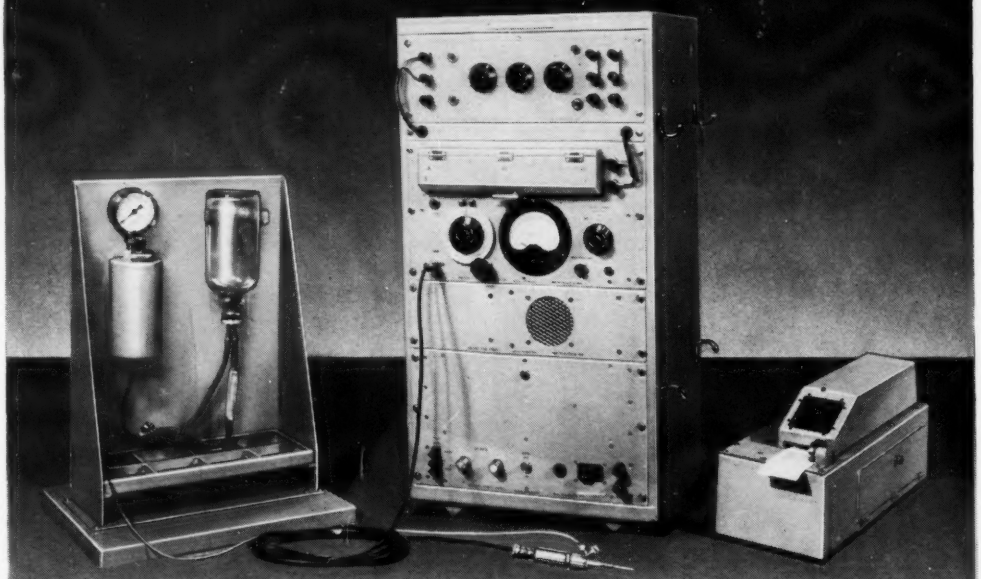

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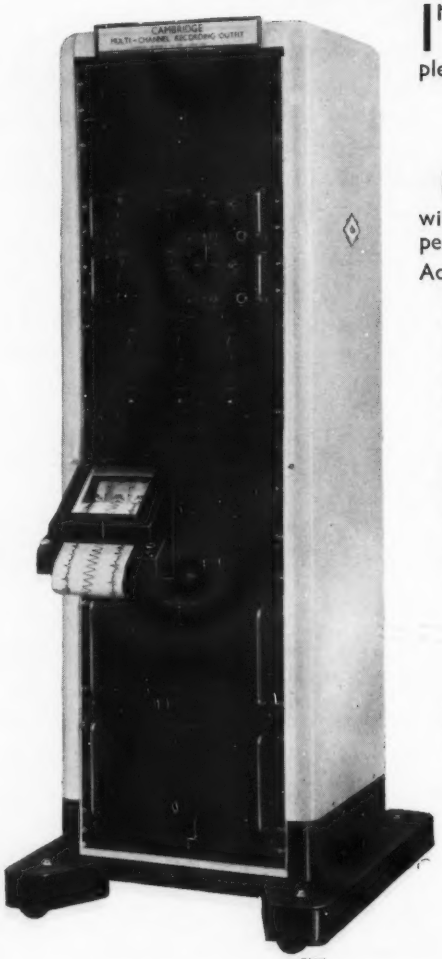

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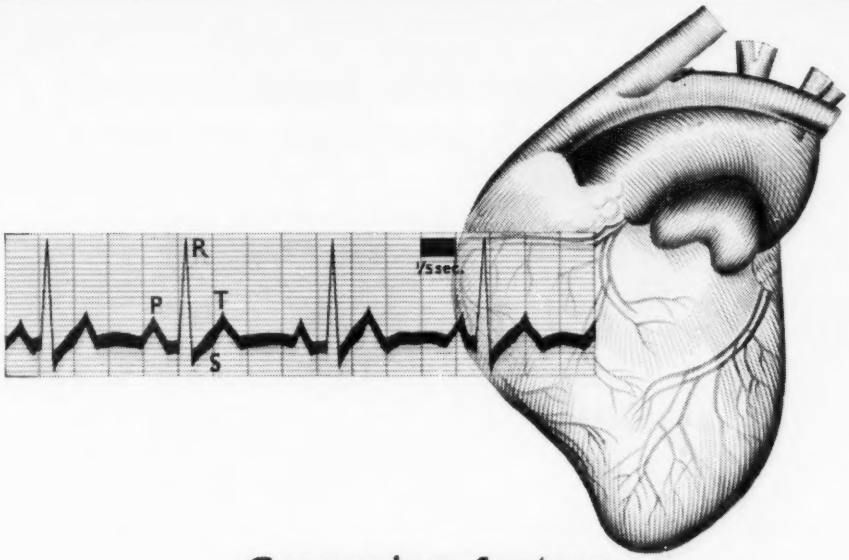

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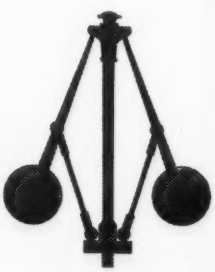

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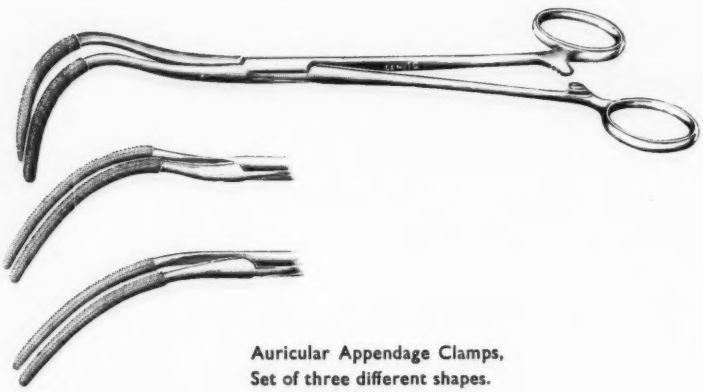

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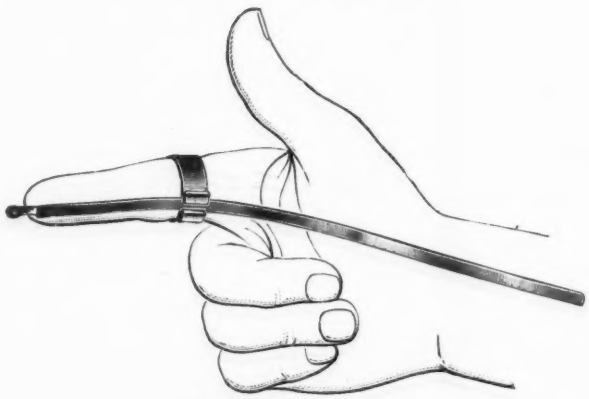

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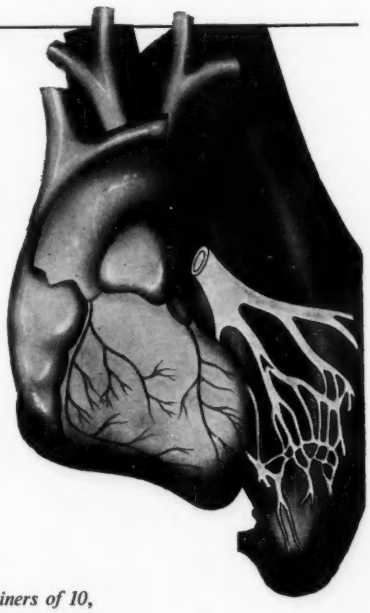

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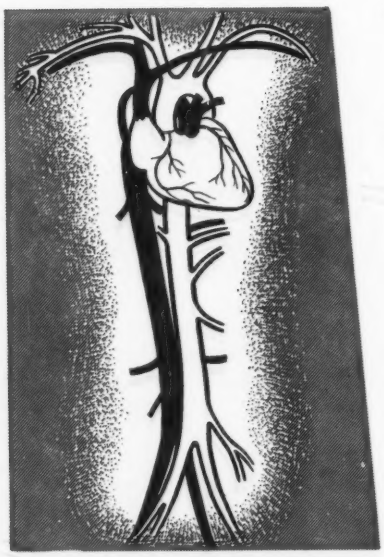
PHENYLINDANEDIONE
(DUNCAN)

Duncan

By retarding prothrombin production, Phenylindanedione prolongs blood coagulation time. Extension of any thrombus formed is prevented, and clot elimination facilitated.

Superior to other anti-coagulants, Phenylindanedione readily maintains a therapeutic prothrombin level, its rapid action and excretion minimising accumulation and individual susceptibility.



Except in cases of hepatic or renal damage, risk of haemorrhage, or concurrently with salicylates, Phenylindanedione is indicated for thrombosis, embolism and thrombophlebitis.

Containers of 25, 100 and 500 scored tablets of 50 mg.

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For

the patient

with angina

Peritrate is a valuable aid in the treatment of angina by virtue of its action as a coronary vasodilator. Each 10 mg. tablet begins to act half-an-hour after ingestion and the action continues 4-5 hours. Peritrate prevents anginal attacks, or reduces their frequency, severity and duration. It diminishes the patient's nitroglycerin requirements, and improves exercise tolerance. Peritrate is non-toxic and causes very few side-effects even on prolonged administration.

PERITRATE WITH PHENOBARBITONE

Peritrate is now available with Phenobarbitone for the Angina Pectoris patient who needs sedation. Each tablet contains 10 mg. Peritrate and 15 mg. Phenobarbitone.

Peritrate

Trade Mark

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AND PERITRATE WITH PHENOBARBITONE

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Packs: *Bottles of 50 and 500. Bottles of 500 tablets are supplied to chemists at 9/- not subject to P.T.*

Peritrate with Phenobarbitone is supplied at the same price as Peritrate, plus 2/3 P.T.

Further information is available on request.

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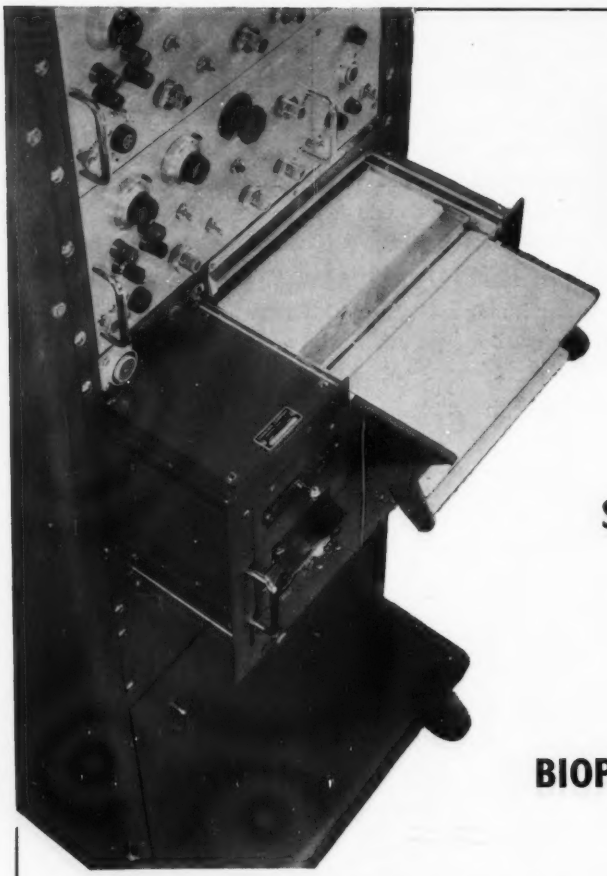

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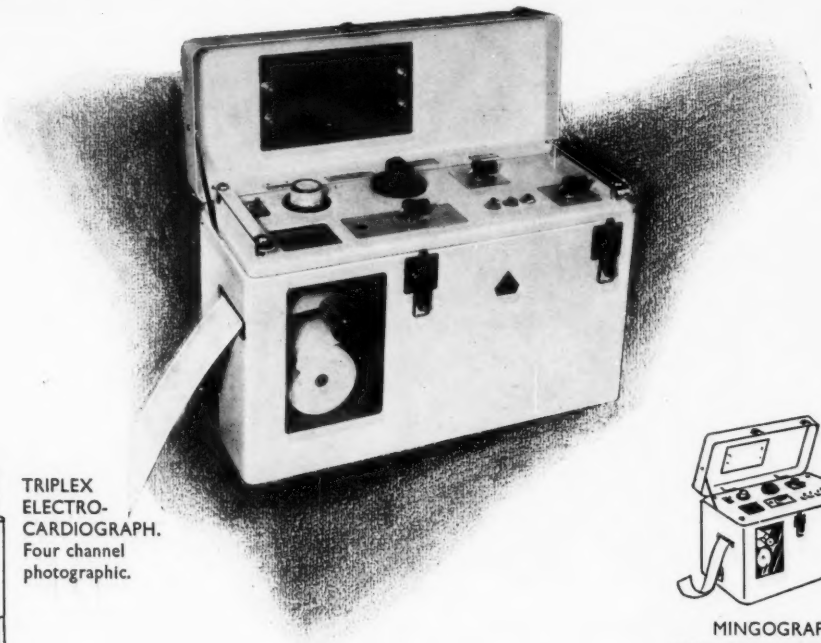

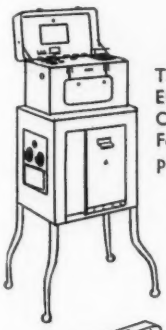

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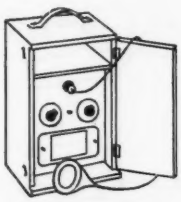

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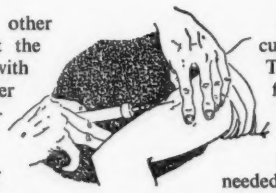

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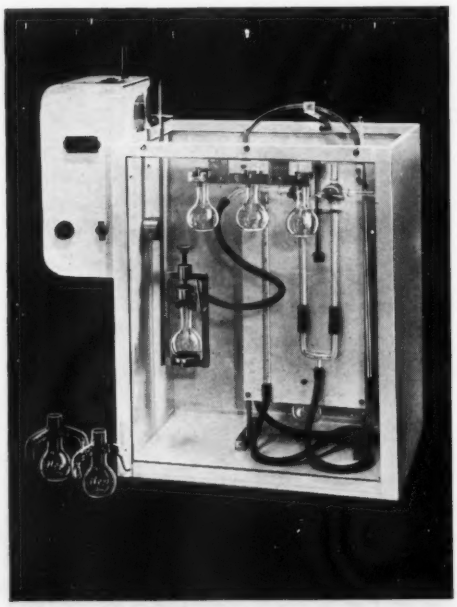

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